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DIENST GENEESKUNDIGE VERZORGING
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The management of heart failure

Literature review: full report

Consensus conference
November 28th 2024
Auditorium Lippens (Royal Library)
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This literature review was performed by BCFI/CBIP

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Table of contents

1 Abbreviations

ACE-I: angiotensin conversion enzyme inhibitor
AF: atrial fibrillation
ARB: angiotensin receptor blocker
ARNI: angiotensin receptor neprilysin inhibitor
BMI: body mass index
CHD: coronary heart disease
CI: confidence interval
CKD: chronic kidney disease
COPD: chronic obstructive pulmonary disease
CV: cardiovascular
CVA: cerebrovascular accident
CVD: cardiovascular disease
DB: double blind
DM: diabetes mellitus
eGFR: estimated glomerular filtration rate
HF: heart failure
HFmrEF: heart failure with mid-range ejection fraction
HFpEF: heart failure with preserved ejection fraction
HFrEF: heart failure with reduced ejection fraction
HHF: hospitalization for heart failure
HR: hazard ratio
ITT: intention-to-treat analysis
KCCQ: Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire – clinical summary score
KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire – total symptom score
MA: meta-analysis
MCID: minimal clinically important difference
MD: mean difference
MI: myocardial infarction
MRA: mineralocorticoid receptor antagonist
n: number of patients
N: number of studies
NA: not applicable
NR: not reported
NS: not statistically significant
NYHA: New York Heart Association
OL: open label
PG: parallel group
PO: primary outcome
QoL: Quality of life
SB: single blind

SD: standard deviation
SGLT2i: sodium glucose cotransporter-2 inhibitors
SMD: standardized mean difference
SR: systematic review
SS: statistically significant
T2DM: type 2 diabetes mellitus
WOREL: Werkgroep Ontwikkeling Richtlijnen Eerste Lijn

2 Methodology

2.1 Introduction

This systematic literature review was conducted in preparation of the consensus conference **"Management of heart failure"** which will take place on November 28th 2024.

2.2 Questions to the jury

The questions to the jury to be considered in this literature report, as they were phrased by the organising committee of the RIZIV/INAMI are:

4) Risk populations

Risk populations were defined as patients with heart failure and one of the following comorbidities:

- diabetes mellitus type II
- morbid obesity
- cachexia or sarcopenia
- severe COPD or pulmonary hypertension
- chronic kidney disease
- atrial fibrillation

The following jury questions apply to each one of the defined comorbidities:

4.1. What specific adjustment in treatment is needed in this population?

4.2. What specific follow-up is needed in this population?

4.3. What specific alarm symptoms are present in this population?

4.4. Are there specific adjustments to reimbursement requirements desirable for this population?

2.3 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss **selected guidelines**.
  - See 2.3.1 for guideline inclusion criteria.
- To perform a literature review:
  - To search and report relevant **RCTs or systematic reviews/meta-analyses of RCTs.**
  - See 2.3.2 for information on study type inclusion criteria and 2.3.3 for search details.
  - To discuss information from **additional sources** for information on safety, contra-indications, specific subgroups, precautions and monitoring.
- See section "Additional safety information from other sources".

In the table below, we provide an overview of the research task of the literature group per jury question. We also indicate in what chapter the results can be found.

(1) Pharmacological treatment of patients with heart failure AND comorbidity

- **Heart failure + Diabetes Mellitus type II**

Information from literature search (chapter 6) , guidelines (chapter 5), safety sources (chapter 11)

- **Heart failure + morbid obesity**

Information from literature search (chapter 8), guidelines (chapter 5), safety sources (chapter 11)

- **Heart failure + severe COPD**

Information from literature search (chapter 9) , guidelines (chapter 5), safety sources (chapter 11)

- **Heart failure + pulmonary hypertension**

Information from literature search (chapter 10), guidelines (chapter 5), safety sources (chapter 11)

- **Heart failure + chronic kidney disease**

Information from literature search (chapter 7), guidelines (chapter 5), safety sources (chapter 11)

- **Heart failure + cachexia or sarcopenia**

Information from literature search (chapter 10), guidelines (chapter 5), safety sources (chapter 11)

- **Heart failure + atrial fibrillation**

Information from guidelines (chapter 5), safety sources (chapter 11)

2.3.1 Guidelines

For the 2024 update of the guideline Heart failure(1), WOREL followed the ADAPTE-procedure. Other guidelines on the management of heart failure were searched by WOREL systematically and the methodological quality was evaluated using the AGREE-instrument.
The following guidelines were selected:

1. Chronic heart failure in adults: diagnosis and management (NG106) (2018) NICE(2)
2. Standaard Hartfalen NHG 2021(3)
3. Chronische Herzinsuffizienz Nationale Versorgungsleitlinie (NVL) (2019) AWMF/KVB/Bundesartzenkammer German(4)
4. Guidelines for the diagnosis and treatment of acute and chronic heart failure (2021) ESC(5)
5. Guideline for the Management of Heart Failure (2022) AHA/ACC/HFSA(6)

The literature group of the Consensus conference will utilize these guidelines and their updates for recommendations and important information, to answer the clinical questions regarding heart failure and comorbidity.
Similarities and discrepancies between guidelines are to be reported.

2.3.2 Study types

We will look at RCTs and systematic reviews and meta-analyses of RCTs.
To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search in multiple databases
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

If some of the included studies in a meta-analysis do not match all the inclusion criteria for our Consensus Conference literature review (for example: it may include some studies with a small sample size, or studies with drugs that are not on the Belgian market), this meta-analysis may be included in our review if judged to be sufficiently relevant. In this case, the discrepancies with our inclusion criteria will be discussed clearly.

RCT's

- Research question matches research question for this literature review
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- Phase III trials (no phase II trials)

Other sources for safety, contra-indications, specific subgroups, precautions and monitoring

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI) / Centre Belge d'Information Pharmacothérapeutique
    - *Gecommentarieerd geneesmiddelenrepertorium/ Répertoire Commenté des Médicaments*(CBIP)(7)
    - *Folia Pharmacotherapeutica*
- Martindale: The complete drug reference (online)(8)

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English
- Unpublished studies

2.3.3 Specific search criteria

2.3.3.1 Pharmacological treatment of patients with heart failure + comorbidity

	Inclusion	Exclusion
Population	Patients with chronic heart failure (HFrEF, HFmrEF, HFpEF) **+ comorbidity** a. Diabetes Mellitus type II b. Morbid obesity c. Severe COPD d. Pulmonary hypertension e. Chronic kidney disease f. Cachexia or sarcopenia	Patients at high risk for heart failure (primary prevention of heart failure) RCTs including <100% heart failure patients (non-heart failure-first trials) Oncological patients Patients hospitalized for decompensated heart failure Patients with end-stage renal disease and/or on renal replacement therapy
Intervention	**SGLT2-inhibitors, gliflozins** • *Canagliflozin** • Dapagliflozin • Empagliflozin **Angiotensin Receptor-Neprilysin Inhibitor (ARNI)** • Sacubitril/valsartan complex **Mineralocorticoid receptor antagonists (MRA)** • Eplerenone • Spironolactone • *Finerenone** *does not have the indication heart failure	**HF not yet a registered indication** GLP-1-analogues **Not in ambulant setting** Digitalisglycosides Nitrates Milrinon Levosimendan Dobutamin
Comparison	• Placebo • Each other • Other heart failure therapy/ standard medical therapy	
Outcome	patients' quality of life, exercise capacity, HF hospitalizations, mortality, adverse effects, patient adherence Comorbidity endpoints: to be defined by comorbidity; hard endpoints	
Study design	RCTs • Minimum 40 participants per treatment arm	Observational studies Open label

	• Minimum treatment duration of 12 weeks Systematic review of RCTs	Phase 2 studies

2.4 Search strategy

2.4.1 Principles of systematic search

*Relevant RCTs, meta-analyses and systematic review*s were searched in a stepwise approach.
In a first step we search for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library, systematic reviews from included guidelines) that answer some or all of our research questions. One or more systematic reviews were selected as our basic source. From these sources, all references of relevant publications were screened manually.
In a second step, we conducted a systematic search in the Medline (PubMed) electronic database for randomised controlled trials (RCTs), meta-analyses, systematic reviews that were published after the search date of our selected systematic reviews.
For all research questions, a search string was developed to search Medline via Pubmed from inception up until July 1st 2024.

2.4.2 Search strategy details

The full search strategies can be found in the appendix.

2.5 Selection procedure

A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was retrieved to decide on inclusion or exclusion.
Unclear eligibility for inclusion was resolved through discussion with a second researcher.
In - and exclusion criteria of the different types of studies are found in "2.3.3. Specific search criteria" with relevant populations, interventions, endpoints and study criteria.
The selection of the studied populations and interventions was based on discussions between the literature group and the Organisation Committee.
The list of articles excluded after reading of the full text can be found in the appendix.

2.6 Assessing the quality of available evidence

2.6.1 Assessing subgroup analyses

To assess the credibility of subgroup analyses, a specific approach should be used. No formal appraisal tool for subgroup analyses yet exists.

Minerva, in 2010(9), cited a checklist of 11 items to check for the credibility of subgroup analysis, developed by Sun 2010(10). This list was later revised to 10 items by the same authors through discussions with a consensus group. See table for the ten criteria as described by Sun 2012(11).

Ten criteria used to assess credibility of subgroup effect (Sun 2012(11))
Design
• Was the subgroup variable a baseline characteristic? • Was the subgroup variable a stratification factor at randomisation? • Was the subgroup hypothesis specified a priori? • Was the subgroup analysis one of a small number of subgroup hypotheses tested (≤5)?
Analysis
• Was the test of interaction significant (interaction P <0.05)? • Was the significant interaction effect independent, if there were multiple significant interactions?
Context
• Was the direction of subgroup effect correctly prespecified? • Was the subgroup effect consistent with evidence from previous related studies? • Was the subgroup effect consistent across related outcomes? • Was there any indirect evidence to support the apparent subgroup effect—for example, biological rationale, laboratory tests, animal studies?

Of these items, Sun considers three items as critical. Only when all three, and most of the others, are answered positively, can one consider to take the subgroup effect into account in clinical practice.

- **Was the subgroup variable a baseline characteristic?**
- **Was the subgroup hypothesis specified a priori?**
- **Was the test of interaction significant (interaction P <0.05)?**

In absence of a credible subgroup effect, the overall effect of the study applies.

In assessing the different criteria, we have applied the following rules:

- We will answer the three critical questions (as described above) for each one of the reported subgroup analyses.
- Only when all three are answered positively, we will do a full assessment of the credibility of the subgroup effect (all 10 questions). An overall assessment of the confidence that can be placed in the subgroup analysis will be assigned. These judgements range from an assessment of 'very low confidence' to high confidence'(12).
- When the subgroup analysis is deemed not credible, the overall effect of the study is reported and appraised via the GRADE methodology (see next chapter).

2.6.2 Assessing overall outcomes via GRADE

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.

The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.
The GRADE system assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed.
In assessing the different criteria, we have applied the following rules:

Study design

In this literature review RCT's and observational studies are included. RCTs start out as high quality of evidence (4 points), observational studies start out as low quality of evidence (2 points). Points can be deducted for items that are assessed as having a high risk of bias.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:

Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.

For example:

> Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
>
> A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account:

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point can be deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤0.75 to ≥1.25).

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

2.7 Synopsis of the study results

The complete report contains:

- (Comprehensive) summary of selected guidelines.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English).
- An appendix, containing evidence tables of systematic reviews or RCTs on which the answers to the study questions are based, full search strategies and excluded references.

The synopsis report contains:

- (Brief) summary of selected guidelines.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

3 Critical reflections of the literature group

3.1 Rationale of the review

The update of the WOREL guideline “Heart Failure”(1), published in 2024, has previously made recommendations through an exhaustive search, assessment of the literature, and consensus process, on the use of the newer medications (SGLT2-i, MRA, ARNI) in heart failure patients in a Belgian health care context.

For this review, we were tasked to search and summarize the evidence on these medications in heart failure patients with specific comorbidities (diabetes mellitus type 2, chronic kidney disease, severe COPD, morbid obesity, cachexia or sarcopenia).

The question to the jury is whether there are sufficiently important differences (of efficacy, safety, applicability, ...) in patients with certain comorbidities to suggest adjustments or additional precautions of the recommended treatment.

3.2 Remarks on methodology

3.2.1 Systematic reviews

We performed an initial search for systematic reviews that corresponded one or more of our search questions.

Although we did find systematic reviews, they often did not sufficiently answer our questions or did not meet our methodological criteria. Populations were pooled that we wanted to assess separately (e.g., HFrEF and HFpEF), and interventions that were not available in Belgium (such as sotagliflozin) were pooled with other interventions in their class.

Because of the nature of our population of interest, it also often involves pooling of subgroup analyses, compromising the assessment of credibility (See next section on subgroup analyses). Therefore, we elected to report the RCTs (and their subgroup analyses) separately.

3.2.2 Subgroup analyses

Since no RCTs were found that evaluated the interventions of interest in a population consisting entirely of heart failure patients with any of the comorbidities of interest, we reported **subgroup analyses** of the major studies in patients with heart failure.

The purpose of a subgroup analysis is to evaluate whether the effect of a treatment varies across subgroups (defined by patient characteristics such as diabetes status).

Often, the effects observed within individual subgroups are misinterpreted. For instance, if a treatment shows a statistically significant result in the overall population but not in a specific subgroup, it may be wrongly assumed that the treatment has no effect in that subgroup. This could simply be due to the smaller sample size of the subgroup.

A more accurate approach is to use an interaction test, which statistically examines whether the subgroups influence the treatment's effect on the outcome, providing **a p-value for the interaction.** To avoid this misinterpretation, we have always reported the p-value for interaction and not the individual subgroup effects in our synopsis report.

Subgroup analyses often produce misleading conclusions due to chance findings, especially when multiple comparisons are made without appropriate adjustments. In most cases, an effect from a subgroup analysis can only be considered exploratory and hypothesis-generating.

The risk lies in making clinical decisions based on spurious subgroup analyses and unfairly withholding or recommending a drug to a particular patient group. A highly critical attitude toward subgroup analyses is necessary, especially when considering them in clinical decision-making.

3.3 Remarks on the results of the literature review

3.3.1 Type 2 diabetes

Results from subgroup analyses suggest that diabetes status does not modify the effect of dapagliflozin, empagliflozin, eplerenone, spironolactone, or sacubitril/valsartan in patients with heart failure.

Diabetes patients are generally well represented in these heart failure studies, with around 50% of the studied population having diabetes.

3.3.2 Chronic kidney disease

Results from subgroup analyses suggest that CKD status does not modify the effect of dapagliflozin, empagliflozin, eplerenone, spironolactone, or sacubitril/valsartan in patients with heart failure. There may be a difference in the effect of empagliflozin on the eGFR slope (rate of decline) in CKD patients versus non-CKD patients. In CKD patients the slowing of the slope may be less pronounced than in non-CKD patients. The clinical importance of this effect is likely limited, as the direction of the effect is the same as in the overall group (in favour of empagliflozin).

Most RCTs excluded patients with a baseline eGFR <30 mL/min/1.73m², so we cannot draw conclusions for this patient group.

In most studies, CKD status was defined as eGFR ≥60 mL/min/1.73m² versus <60 mL/min/1.73m². In some studies, a more granular categorization was used in addition, with 3 to 5 eGFR categories. The subgroup effects (or lack thereof) seemed consistent in both categorizations.

3.3.3 Obesity

We were tasked to report especially on morbid obesity (or class 2 and 3 obesity); defined as a BMI≥35. However, subgroup analyses for BMI prespecified in the protocols of the heart failure studies commonly classified BMI as <30 and BMI≥30 kg/m².

In the main publications of these heart failure trials subgroup analysis according to BMI is often included, but without the interaction p-value which is required to evaluate heterogeneity of efficacy. Several additional publications evaluated the relation between baseline BMI and outcomes in patients enrolled in large heart failure trials that evaluated SGLT2-inhibitors and mineralocorticoid receptor antagonists.

Susceptibility to obesity-related cardiovascular complications is not mediated solely by overall body fat mass. Therefore, some analyses also evaluated abdominal obesity at baseline estimated by waist circumference.

With the exception of one study (Elkholey 2021(13)), all subgroup analyses used a more detailed categorization of BMI than prespecified in the protocol and analyses were performed for outcomes that were not always prespecified in the protocol. Patients with BMI≥35 represent a smaller subset of the overall population (10-20%).The p-values for the subgroup analyses and interaction were not adjusted for multiple comparisons. These limitations impact the interpretation of the results.

3.3.4 Chronic obstructive pulmonary disease

We were tasked to report especially on severe COPD. However, in two studies on sacubitril/valsartan (PARADIGM-HF(14) and PARAGON-HF(15)), patients with severe pulmonary disease, including severe COPD, were excluded from the trial.

In one other study evaluating dapagliflozin (Dewan 2021(16)), COPD status was based on investigator-reported medical history; it was not formally diagnosed or evaluated at baseline in any studies; and no indication of severity was recorded.

3.3.5 Pulmonary hypertension

Our search did not yield results corresponding to our inclusion criteria.

3.3.6 Cachexia, sarcopenia

Our search did not yield results corresponding to our inclusion criteria.

3.4 Remarks on the recommendations from guidelines

The guidelines were selected by WOREL in the context of the WOREL guideline "Heart failure"(1), and we refer to WOREL for their quality assessment.
We reported recommendations about pharmacological treatment in heart failure patients with comorbidities (type 2 diabetes, chronic kidney disease, (morbid) obesity, (severe) COPD, pulmonary hypertension, cachexia or sarcopenia).

For heart failure with atrial fibrillation (AF): only the recommendations concerning the safety and interactions of the drug treatment (in both conditions) are reported. The management of patients with HF and AF was considered specialized treatment by the Organizing Committee.

We did **not** report standard treatment recommendations for a population of heart failure patients without comorbidity. For these, we refer to the WOREL guideline "Heart failure".

We did **not** report recommendations on the **prevention of heart failure** (in a population currently without HF), with the exception of the recent recommendations from the ESC 2023 update or those about recent drug advances such as SGLT2i.

Generally speaking, there are no major contradictions between the guidelines with regards to approaches in case of comorbidity or the safety of treatment in these conditions.

All the guidelines (except NICE 2018 who has not yet included recommendations on SGLT2i) acknowledge the benefit of SGLT2i and are favorable to their use for patient with HF and type 2 diabetes, although with different levels of recommendation.

None of the guidelines have formulated recommendations concerning SGLT2i in the context of HF and CKD except the focused update ESC 2023 that recommends SGLT2 inhibitors (and finerenone) in patients with T2DM and CKD to reduce the risk of HF hospitalization or CV death.

Guideline updates

Several drugs, such as SGLT2i, are recent additions to heart failure treatment. Topic experts raised the introduction of these drugs as key developments in the field that are changing clinical practice. This requires revision of the guidelines. Several of the selected guidelines have recently received updates, or are currently in revision. We have used the most current recommendations where possible.

- NVL 2023(4) is an updated version of the NVL 2019 that is included in the WOREL guideline. Only the drug therapy chapter is updated for the moment due to its high relevance for care. The current version 4 was integrated into the existing chapters of the previous edition (2019). This version 4 is formally valid until the end of 2024. **The publication of version 5 of the guideline is planned for 2024, when all chapters will be updated (not yet published).**
- ESC 2021(5) is the version included in the WOREL guideline. ESC has published a focused update in 2023(17) including important new trials. Some additional recommendations have been made for HFmrEF and HFpEF taking these trials into account. The Focused 2023 update has been included in our document as well as the ESC 2021 version.

- NICE assessed that the recommendations on pharmacological treatments of HFrEF in the NICE 2018(2) guideline are out of date when compared to 2021 ESC guideline and to current UK clinical practice. A new guideline is in development and will be a partial update of the current one. **This new guideline is still in progress.**
- NHG 2021(3) has been summarised in the present document. A full and recent revision of this guideline was published in September 2024 (during the revision period of this full document). In order to be as up-to-date as possible, new recommendations concerning SGLT2 inhibitors have additionally been included in this document. In order to show the chronological evolution, we have not deleted the corresponding recommendations made in the previous 2021 version. It has been clearly indicated when a recommendation comes from the updated 2024 version.

3.5 Remarks on safety information

It is difficult to draw conclusions from adverse events reported in RCTs, since they are usually set up in a way to minimize adverse events (for example, by excluding patients with a high risk of adverse events).

Some adverse events are rare occurrences. The less common they are, the longer and/or larger the studies need to be to identify a difference between active and control group.

Subgroups are often not adequately powered to assess for differences in adverse events, and are thus often (appropriately) not analyzed for this purpose.

In the chapter “Additional safety information from other sources”, we report information from BCFI/CBIP sources and from Martindale: The complete drug reference (online) as an addition to the information that was reported in the studies included in our review.

In this chapter we also list possible **interactions** between medication used in heart failure and in the comorbidities.

4 General information on selected guidelines

4.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in the following table.

Abbreviation	Guideline
AHA/ACC/HFSA 2022(6)	2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines
ESC 2021(5)	2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
NHG 2021(3)	NHG-STANDAARD Hartfalen, KNR nummer M51, mei 2021
NICE 2018(2)	Chronic heart failure in adults: diagnosis and management NICE guideline [NG106]-12 September 2018
NVL 2023(4)	Chronische Herzinsuffizienz, Nationale Versorgungsleitlinie (NVL) AWMF/KVB/Bundesartzenkammer, Version 4.0 AWMF-Register-Nr. nvl-006

4.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in the following tables.

AHA/ACC/HFSA 2022		
Class of Recommendation (COR): (indicates the strength of recommendation)	Class 1	Strong recommendation: benefit >>> risk
	Class 2a	Moderate recommendation: benefit >> risk
	Class 2b	Weak recommendation: benefit ≥ risk
	Class 3 no benefit	Moderate recommendation against: benefit = risk
	Class 3 harm	Strong recommendation against: risk > benefit
Levels of evidence	A	High quality evidence from more than 1 RCT or MA of high quality RCTs or One or more RCT corroborated by high quality registry studies

	B-R	Moderate quality evidence from 1 or more RCTs or MA of moderate quality RCTs
	B-NR	Moderate quality evidence from 1 or more well-designed, well-executed non-randomized studies, observational or registry studies or MA of such studies
	C-LD	Randomized or non-randomized observational or registry studies with limitations of design or execution or MA of such studies or Physiological or mechanistic studies in human
	C-EO	Consensus of expert opinion based on clinical experience

ESC 2021		
Class of Recommendation (COR):	Class I (worded as 'Is recommended or is indicated')	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
	Class IIa (worded as 'Should be considered')	Weight of evidence/opinion is in favour of usefulness/efficacy.
	Class IIb (worded as 'May be considered')	Usefulness/efficacy is less well established by evidence/opinion.
	Class III (worded as 'Is not recommended')	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.
Levels of evidence	A	Data derived from multiple randomized clinical trials or meta-analyses.
	B	Data derived from a single randomized clinical trial or large non-randomized studies.

	C	Consensus of opinion of the experts and/or small studies,retrospective studies, registries.

NHG 2021		
Grades of recommendation:	STERK VOOR (worded as 'We bevelen [interventie] aan')	De voordelen zijn groter dan de nadelen voor bijna alle patiënten. Alle of nagenoeg alle geïnformeerde patiënten zullen waarschijnlijk deze optie kiezen
	ZWAK VOOR (worded as 'Overweeg [interventie], bespreek de voor- en nadelen').	De voordelen zijn groter dan de nadelen voor een meerderheid van de patiënten, maar niet voor iedereen. De meerderheid van de geïnformeerde patiënten zal waarschijnlijk deze optie kiezen.
	ZWAK TEGEN (worded as 'Wees terughoudend met [interventie], bespreek de voor- en nadelen.')	De nadelen zijn groter dan de voordelen voor een meerderheid van de patiënten, maar niet voor iedereen. De meerderheid van geïnformeerde patiënten zal waarschijnlijk deze optie niet kiezen
	STERK TEGEN (worded as 'We bevelen [interventie] niet aan.')	De nadelen zijn groter dan de voordelen voor bijna alle patiënten. Alle of nagenoeg alle geïnformeerde patiënten zullen waarschijnlijk deze optie niet kiezen
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE), NHG does not explicitly attribute levels of evidence to each particular recommendation.	

NICE 2021		
Grades of recommendation:	Interventions that must (or must not) be used worded as such in the text.	Generally used if there is a legal duty to apply the recommendation. But used as well if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Intervention that should (or should not) be used are worded in the text using the term "offer", "refer", "advise" or similar…	There is clear evidence of benefit. We are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective.
	Intervention that could (or could not) be used are worded in the text using the term "consider"	Reflects a recommendation for which the evidence of benefit is less certain. We are confident that an intervention will do more good than harm for most patients, and be

		cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE, CASP RCT, cohort study, case-control checklists, CERQual) NICE does not explicitly attribute strength levels to each particular recommendation.	

NVL 2023		
Grades of Recommendation	A↑↑ (Formulated as 'soll')	Starke Positiv-Empfehlung: Bei starken Empfehlungen sind sich die Leitlinienautoren in ihrer Einschätzung sicher. Starke Empfeh-lungen drücken aus, dass die wünschenswerten Folgen mit hoher Wahrscheinlichkeit mögliche unerwünsch-te Effekte in Bezug auf patientenrelevante Endpunkte überwiegen.
	B↑ (Formulated as 'sollte')	Abgeschwächte Positiv-Empfehlung: Bei abgeschwächten Empfehlungen sind sich die Leitlinienautoren in ihrer Einschätzung weniger si-cher.
	0↔ (formulated as 'kann erwogen werden/kann verzichtet werden')	Offene Empfehlung: Bei offenen Empfehlungen sind sich die Leitlinienautoren nicht sicher. Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus.
	B↓ (formulated as 'sollte nicht')	Abgeschwächte Negativ-Empfehlung
	A↓↓ (formulated as 'soll nicht')	Starke Negativ-Empfehlung Bei starken Empfehlungen sind sich die Leitlinienautoren in ihrer Einschätzung sicher
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE), NVL 2023 does not explicitly attribute levels of evidence to each particular recommendation	

4.3 Agree II score

WOREL conducted a full AGREE II evaluation of the selected guidelines. The table below shows the scores on the subdomains.

	NICE	NHG	AWMF/KVB/BK	ESC	AHA/ACC/HFSA
Onderwerp en doel	21	19	17	19	21
Betrokkenheid van belanghebbenden	19	21	19	19	20
Methodologie	56	53	43	42	50
Helderheid en presentatie	21	21	18	21	21
Toepassing	28	20	16	19	15
Onafhankelijkheid van opstellers	11	14	11	13	13

4.4 Included populations – interventions – main outcomes

In the following tables, the populations, interventions and main outcomes considered in the selected guidelines are represented.

AHA/ACC/HFSA 2022	
Population	Patients with : heart failure; heart failure with reduced ejection fraction; heart failure with preserved ejection fraction; heart failure with mildly reduced ejection fraction; systolic heart failure; acute decompensated heart failure; cardiogenic shock; cardiac amyloidosis, congestive heart failure
Interventions	Heart failure rehabilitation, beta blockers; mineralocorticoid receptor antagonists, ACE-inhibitors, angiotensin and neprilysin receptor antagonist; sacubitril valsartan; angiotensin receptor antagonist; sodium glucose co-transporter 2 or SGLT2 inhibitors
Outcomes	• Prevention of HF. • Management strategies in stage C HF, including: - New treatment strategies in HF, including sodium-glucose cotransporter-2 inhibitors (SGLT2i) and angiotensin receptor-neprilysin inhibitors (ARNi). - Management of HF and atrial fibrillation (AF), including ablation of AF. - Management of HF and secondary MR, including MV transcatheter edge-to-edge repair. • Specific management strategies, including: - Cardiac amyloidosis. - Cardio-oncology. • Implantable devices. • Left ventricular assist device (LVAD) use in stage D HF

ESC 2021	
Population	People with HF
Interventions	Pharmacological treatments: • ACE-I • ARNI • Beta-blockers • MRA • SGLT2 inhibitor • Loop diuretics • ARB • Ivabradine • Vericiguat. • Digoxin • Hydralazine/Isosorbide dinitrate Cardiacmyosin activator

	Cardiac rhythm management : - Implantable cardioverterdefibrillator - Cardiac resynchronization therapy Exercise rehabilitation
Outcomes	Focus on diagnosis and treatment of HF not on its prevention

NHG 2021	
Population	Volwassenen met: chronisch hartfalen (geleidelijk ontstaan) acuut hartfalen (ontstaan of verergerd in enkele uren), exacerbatie van chronisch hartfalen Excluded: Systolische of diastolische linkerventrikeldisfunctie zonder klachten passend bij hartfalen (kan een voorstadium van hartfalen zijn).
Interventions	Vocht- en zoutbeperking Beweging Leefstijl Medicamenteuze behandeling : • Diuretica • Bètablokkers • Aldosteronantagonisten • ACE-remmer • ARB • Digoxine • SGLT-2 -remmers • Angiotensinereceptor-neprilysineremmers • Ivabradine
Outcomes	Diagnostiek en behandeling van hartfalen bij volwassenen Sterfte, alle oorzaken Sterfte, cardiovasculaire oorzaak Kwaliteit van leven Ongeplande ziekenhuisopname wegens hartfalen Nierfunctie Bijwerkingen:

NICE 2018	
Population	Adults (18 and over) with symptoms or a diagnosis of chronic heart failure (including heart failure with reduced ejection fraction and heart failure with preserved ejection fraction). Not covered: - Diagnostic screening for heart failure in people who are asymptomatic. - People with isolated right heart failure. - Heart failure in people having chemotherapy. - Heart failure in people having treatment for HIV.

	- Heart failure in women who are pregnant. - People with iron deficiency. - People with chronic kidney disease (estimated glomerular filtration rate [eGFR] less than 60 ml/min/1.73m2 with or without markers of kidney damage). - People with chronic heart failure and secondary atrial fibrillation. - People aged over 75.
Interventions	Pharmacological therapies including: – Isosorbide/hydralazine. – Angiotensin-II receptor antagonists (ARBs). – Mineralocorticoid receptor antagonists Not covered: beta-blockers in people with chronic heart failure and secondary atrial fibrillation.
Outcomes	Diagnosing heart failure. o Role of circulating biomarkers (including natriuretic peptides). o Echocardiography and cardiac MRI. Managing chronic heart failure. o Initiation and sequencing of pharmacological therapies o Fluid balance (optimum fluid and salt intake). Rehabilitation (including Home-based rehabilitation packages that include an exercise element). Monitoring heart failure. o Role of biomarkers (including natriuretic peptides). o Role of echocardiography. o Distance monitoring including telemonitoring. o Self-monitoring. Referral for invasive procedures: o Coronary revascularisation (including coronary artery bypass graft and angioplasty). Referral and approach to care. o Heart failure multidisciplinary team. o Transfer of care between secondary and primary care services. Information and support. o Information and support on diagnosis and prognosis for people with chronic heart failure, their families and carers. Supportive and palliative care. o Domiciliary oxygen therapy.

	o Parenteral and intravenous diuretics. o Criteria for withdrawing treatment and device inactivation

NVL 2023	
Population	Die NVL Chronische Herzinsuffizienz befasst sich mit der Versorgung von Patient*innen mit Links- und Global-herzinsuffizienz inklusive akuter Dekompensationen (siehe Kapitel 1 Definition und Klassifikation (2019)). Isolierte Rechtsherzinsuffizienz wird in dieser Leitlinie nicht abgebildet, da sie ein grundsätzlich anderes Vorgehen erfordert.
Interventions	In addition to information found in their source doc , a systematic search has been conducted for the following interventions: Kapitel Medikamentöse Therapie: - Sacubitril/Valsartan; - Ivabradin; - Spironolacton bei Patienten mit Herzinsuffizienz mit erhaltener Ejektionsfraktion (HFpEF). Kapitel Invasive Therapie: - Komplikationen von ICD und CRT; - Registerdaten ICD und CRT; - ICD und CRT bei älteren Patienten; - CRT bei Patienten mit Vorhofflimmern; - CD in der Sekundärprävention; - Vergleich von Einkammer- vs. Zweikammer-ICD; - Vergleich von CRT-P und CRT-D; - Herzunterstützungssysteme; - Operative/katheterbasierte Therapie der sekundären Mitralklappeninsuffizienz. Kapitel Nicht-medikamentöse Therapie: - Ernährung; - Gewichtsreduktion; - Tabakverzicht; - Alkoholverzicht bzw. -reduktion - körperliche Aktivität/Training; - Schulungen. - Kapitel Komorbiditäten: - Eisensupplementierung (für i.v. Eisensupplementierung zusätzliche Suche nach Spontanmeldungen zur Pharmakovigilanz).
Outcomes	Die NVL Chronische Herzinsuffizienz soll dazu beitragen, folgende Ziele zu erreichen: - Stärkung der patientenzentrierten Versorgung (verbesserte Arzt-Patienten-Kommunikation, gemeinsame Ver-einbarung

	von Therapiezielen, Förderung der Therapieadhärenz, Behandlung am Lebensende gemäß den individuellen Bedürfnissen und Präferenzen des Patienten); - adäquate Therapie der Grunderkrankungen zur Prävention des Entstehens oder der Progression einer chroni-schen Herzinsuffizienz; - implementierung wiederholter edukativer Elemente zur Verbesserung des Selbstmanagements und der Adhä-renz der Patienten in der Langzeitbetreuung; - Optimierung der Therapie zur Vermeidung von Dekompensationen und Krankenhauseinweisungen; - verbesserte Koordination aller an der Versorgung Beteiligten (interdisziplinäre Versorgung, Palliativversor-gung, sektorenübergreifende Versorgung).

4.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the following tables.

AHA/ACC/HFSA 2022	
Development group	The Joint Committee strives to ensure that the guideline writing committee contains requisite content expertise and is representative of the broader cardiovascular community by selection of experts across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and clinical practice settings. Organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators. The writing committee consisted of cardiologists, HF specialists, internists, interventionalists, an electrophysiologist, surgeons, a pharmacist, an advanced nurse practitioner, and 2 lay/patient representatives. The writing committee included representatives from the ACC, AHA, and Heart Failure Society of America (HFSA)
Target audience	The intended primary target audience consists of clinicians who are involved in the care of patients with HF. Recommendations are stated in reference to the patients and their condition. The focus is to provide the most up-to-date evidence to inform the clinician during shared decision-making with the patient.

ESC 2021	
Development group	The Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Clinical Practice Guidelines (CPG) Committee policy.
Target audience	Health professionels

NHG 2021	
Development group	Leden van de werkgroep waren huisartsen, een cardioloog en een afvaardiging van de Harteraad.
Target audience	NHG-richtlijnen zijn richtlijnen voor het handelen van de huisarts bij uiteenlopende klachten en aandoeningen.

NICE 2018	
Development group	A multidisciplinary guideline committee comprising health professionals and researchers as well as lay members developed this guideline (see the list of guideline committee members and the acknowledgements).

Target audience	The guideline update is intended for use by the following people or organisations: - All healthcare professionals - People with chronic heart failure and their carers - Patient support groups - Commissioning organisations - Service providers

NVL 2023	
Development group	Primäre Ansprechpartner innen bei der Benennung von Leitlinienautor innen sind die Mitgliedsgesellschaften der AWMF sowie die Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ). Die an der Versorgung von Menschen mit Chronischer Herzinsuffizienz maßgeblich beteiligten Fachgesellschaften wurden durch das ÄZQ angesprochen und um Entsendung von Mandatsträger innen in die Leitliniengruppe gebeten. Die Nominierung liegt im Verantwor-tungsbereich der angesprochenen medizinischen wissenschaftlichen Fachgesellschaften. Die Leitliniengruppe wurde multidisziplinär zusammengesetzt. Gemäß AWMF-Regelwerk Leitlinien sind Patient innen regelhaft beteiligt an der NVL-Erstellung, am externen Begutachtungsverfahren und an der Erstellung von Patientenleitlinien zur entsprechenden NVL. Die Benennung von Patientenvertreter innen erfolgt nach einem transparenten, standardisierten Verfahren über die Dachverbände der Selbsthilfeorganisationen.

Target audience	Die Empfehlungen Nationaler VersorgungsLeitlinien richten sich an ▪ die Ärztinnen und Ärzte, die in den von der NVL angesprochenen Versorgungsbereichen tätig sind; ▪ die nicht-ärztlichen Fachberufe, die in den von einer NVL angesprochenen Versorgungsbereichen als Kooperationspartner der Ärzteschaft tätig sind (Pflegekräfte, Apotheker*innen); ▪ die betroffenen Patient*innen und ihr persönliches Umfeld. Die NVL wendet sich weiterhin an ▪ die Vertragsverantwortlichen von Strukturierten Behandlungsprogrammen und Integrierter Versorgung; ▪ die medizinischen wissenschaftlichen Fachgesellschaften und andere Herausgeber von Leitlinien; ▪ die Kostenträger im Gesundheitssystem; ▪ die Einrichtungen der ärztlichen Aus-, Fort- und Weiterbildung und an Qualitätsmanagementsysteme; ▪ die breite Öffentlichkeit zur Information über gute medizinische Vorgehensweise.

5 Summary and comparisons of recommendations from guidelines

5.1 General

NICE states that more detailed monitoring will be needed in patients with heart failure if the person has significant comorbidity or if their condition has deteriorated since the previous review.

ESC 2021 recommends **screening for, and treatment of, aetiologies, and CV and non-CV comorbidities in patients with HFpEF**

In HFpEF, in the updated 2024 version, NHG recommends to treat cardiovascular and non-cardiovascular morbidity according to the relevant guidelines.

NVL 2023 makes a general recommendation that in the case of multimorbid patients, complex problems should be prioritized. The therapies for individual diseases are not added together uncritically; instead, the treatment should follow an individual overall concept that takes into account the patient's values, therapy goals and preferences as well as the perspective of the treating physician. It is added that multimorbid and/or elderly patients with chronic heart failure should be offered the therapeutic measures recommended in the S3 guideline Multimorbidity patient-centered care.

NVL 2023 also add a general safety recommendation to critically examine and discuss with the patients the indication of active drugs that may negatively affect the clinical condition or prognosis of patients

with heart failure. A list of medications has been proposed by the guideline group and is reported in regards to each comorbidity.

5.2 Diabetes Mellitus

Prevention of HF

In patients with T2DM at high risk of CV disease or with CV disease: ESC 2021 recommends SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) in order to prevent HF hospitalizations.

In patients with T2DM and CKD, SGLT2 inhibitors and finerenone are recommended in the 2023 upd of ESC to reduce the risk of HF hospitalization or CV death.

In this 2023 upd ESC also mentions that both KDIGO and the *2022 American Diabetes Association Standards of Medical Care in Diabetes and KDIGO* recommendations indicate treatment with an ACE-I or ARB for patients with CKD, diabetes, and hypertension or albuminuria. (effects in preventing HF events in patients with diabetic nephropathy)

Management of patients with HF and diabetes

All the guidelines except NICE 2018 which does not specifically address diabetes are favourable to SGLT2 inhibitors with different degrees of recommendation.

- NHG 2021 recommends to consider an SGLT-2 inhibitor in patients with T2DM and heart failure as these agents lower the risk of heart failure exacerbations. A step-by-step plan has been proposed by NHG Standard Diabetes mellitus type 2.
- AHA/ACC/HFSA 2022 recommends the use of SGLT2i in patients with HF and type 2 diabetes, for the management of hyperglycemia and to reduce HF-related morbidity and mortality.
- ESC 2021 recommends SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.
- NVL 2023 does not make a formal recommendation but notes the following: The initial use of SGLT2 inhibitors appears to the guideline group to be particularly useful in the presence of comorbidities such as diabetes or kidney disease, but also if there is a high risk of progression or if there are contraindications to other prognosis-improving drug groups.

SGLT2 inhibitors in HF

ESC 2021 recommends dapagliflozin or empagliflozin for patient with HFrEF, HFmrEF (upd 2023), or HFpEF (upd 2023) to reduce the risk of HF hospitalization or CV death.

NVL 2023, does not make specific recommendations for patients with T2DM but adopts in the 2023 update the following changes in the general management (without T2DM):

- For HFrEF in addition to the stepwise therapy based on RAS inhibitors and beta-blockers an alternative four-way combination treatment with an additional SGLT2 inhibitor and spironolactone or eplerenone.
- For HFpEF, SGLT2 inhibitors are now the first drug group available with a proven prognosis-improving effect. A SGLT2 inhibitor is recommended.

NVL 2023 notes that to date, there is no evidence for treatment with SGLT2 inhibitors without RASi+beta blockers for heart failure (only for diabetes). It is unclear whether RASi+SGLT2 inhibitors or

beta-blockers+SGLT2 inhibitors would also be effective. Even if only in rare cases, the guideline group itself believes that a primary combination of SGLT2 inhibitors and MRA could be an option. The recommendations therefore deliberately provide a degree of flexibility with regard to the number and type of drug classes used, as long as the treatment is based on patient-relevant criteria.

NHG 2021 does not recommend to start an SGLT-2 inhibitor to treat heart failure in patients **without type 2 diabetes mellitus.***

*In the updated version of NHG published in September 2024:

- It is recommended to start with SGLT2i in HFpEF
- The recommended treatment in HFmrEF and HFrEF consists of (medication step plan): if necessary, a loop diuretic when there are signs of fluid overload, a RAS inhibitor (ACE inhibitor or ARB if necessary), an SGLT2 inhibitor, a beta blocker if necessary; an aldosterone antagonist in case of insufficient effect of the above agents

They also added following recommendations:

- Start an SGLT2 inhibitors in **all new patients** with heart failure
- **In frail patients** with newly diagnosed heart failure: discuss the potential benefits and individual possible risk factors for side effects and make a joint decision on starting an SGLT2 inhibitor
- **In patients with a long-standing history of heart failure** they recommend to discuss starting an SGLT2 inhibitor at the next regular check-up or when they come to the consultation with a heart failure-related complaint.
- In patients with, at the time of symptoms of heart failure, a **NT-proBNP 125-300 pg/ml or BNP 35-50 pg/ml**: consider starting an SGLT2 inhibitor and consult with the cardiologist if necessary. No direct scientific evidence is available for this group. However, a similar effect is plausible.

<u>Safety of drugs in patient with HF and T2DM</u>

In the updated version of NHG published in September 2024, additional precautions to patients with DM2 about lowering other blood sugar-lowering medications (SU derivatives and insulin) and dose adjustment are advised when starting an SGLT2 inhibitor (risk of hypoglycemia).

In this version NHG also mentions that diabetes mellitus type 1 and other situations that confer an increased risk of euglycaemic ketoacidosis, such as alcoholism, malnutrition, intermittent fasting, diet with < 70 grams of carbohydrates per day are contra-indications of SGLT2i.

Glitazones are drugs that should preferably be avoided according to NHG 2021 and are not recommended according to ECS 2021. AHA/ACC/HFSA 2022 considers that **glitazones increase the risk of worsening HF symptoms and hospitalizations, and NVL 2023 notes that it may potentially cause edema.**

Gliptins are drugs that should preferably be avoided according to NHG 2021 and AHA/ACC/HFSA 2022 and are not recommended according to ECS 2021. NVL 2023 also notes that there is an increased risk of angioedema.

NVL 2023 mentions an increased risk of lactic acidosis in decompensated heart failure with metformin. ESC 2021 indicates that metformin is thought to be safe and noticed this risk if eGFR is < 30 ml/min/1.73 m2.

According to ESC 2021, if insulin or sulfonylureas are needed in a patient with HF, the patient should be monitored for evidence of worsening of HF after treatment initiation; sulfonylureas are not a preferred treatment in patients with HF. (not formal recommendations)

NVL 2023 also reports that experience has shown that patients with comorbid diabetes mellitus develop hyperkalemia more frequently when taking ACE inhibitors, ARBs, MRAs and potassium-sparing diuretics. In addition, treatment with beta-blockers can mask the symptoms of hypoglycemia.

ESC 2021 notes that GLP-1 receptor agonists are not recommended for the prevention of HF events. (no effect and/or increased risk) (not formulated as formal recommendation).

5.3 Chronic kidney disease

Prevention of HF

In their 2023 update, ESC recommends SGLT2 inhibitors and finerenone in patients with T2DM and CKD to reduce the risk of HF hospitalization or CV death.

They also mention that both KDIGO and the *2022 American Diabetes Association Standards of Medical Care in Diabetes and KDIGO* recommendations indicate treatment with an ACE-I or ARB for patients with CKD, diabetes, and hypertension or albuminuria. (effects in preventing HF events in patients with diabetic nephropathy)

Management of patients with HF and CKD

- For patients with HFrEF (NICE 2018)/cHF (NVL 2023) and CKD with an eGFR ≥ 30 ml/min/1.73 m2:

  NICE 2018 and NVL 2023 recommend the same drug treatment as for patients with healthy kidneys.

  NICE 2018 also recommends to consider lower doses and/or slower titration of dose of ACE inhibitors or ARBs, MRAs and digoxin if the person's eGFR is 45 ml/min/1.73 m2 or below,

  NICE 2018 notes the following (not formal): The committee agreed that ACE-I should be used as part of first-line treatment, as in the general HFrEF population. The committee noted that ARBs for people with CKD showed only limited benefit, based on the evidence reviewed. The committee reported a lack of clarity about using ACE-I, ARB and MRA in patients with CKD where renal function is declining. They discussed that in these circumstances, total cessation of these medications may deprive patients of the beneficial effects on morbidity and mortality. Therefore, modification to the doses of these agents, or even temporary cessation of one or more agents, should be made based on individual patient circumstances, and guidance from renal physicians should be considered where necessary.

- For patients with HFrEF (NICE 2018)/cHF (NVL 2023) and CKD with an eGFR < 30 ml/min/1.73 m2:

NICE 2018 recommends to consider liaising the specialist heart failure multidisciplinary team **(**MDT) with a renal physician.

NVL 2023 recommends the same drug therapy as patients with healthy kidneys, under consideration of clinical aspects, so long as there are no contraindications (expert consensus based on clinical experience).

In accordance with NICE 2018, NVL 2023 notes the following (not formal): the guideline group considers the risk-benefit ratio (prognosis-improving effects vs. worsened renal function) to be positive and therefore also recommends basic drug therapy with ACE inhibitors or ARBs, beta-receptor blockers and MRA for patients with eGFR < 30 ml/min/1.73 m2, with careful titration and, adjustment of the dosage, with particularly close monitoring of electrolyte balance and kidney function; in consultation with the treating nephrologist.

AHA/ACC/HFSA 2022 notes that the effectiveness of guideline-directed medical therapy (GDMT) in patients with HF and concomitant kidney disease is uncertain, because data for treatment outcomes in this patient population are sparse (not formal recommendation). They recommend that in patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate may be considered to reduce morbidity and mortality. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency.

Safety of drugs in patients with HF and CKD

SGLT2i are contra-indicated in severe renal impairment (dapagliflozin: eGFR < 25ml/min/1.73m2; empagliflozin: eGFR < 20ml/min/1.73 m2) (from the NHG version 2024). If eGFR falls during use of the SGLT2 inhibitor, it is advised to continue it and only discontinue it at the start of dialysis.

Sacubitril/valsartan should not be recommended for patients with cHF and CKD with eGFR < 30 ml/min/1.73 m2. (Patients with eGFR < 30 ml/min/1.73 m2 were excluded from the pivotal study; however, but sacubitril/valsartan is formally approved for these patients; there is little clinical experience.) Spironolactone and eplerenone are contraindicated in patients with severe renal insufficiency (NVL 2023).

NVL 2023 also recommends that in patients with cHF and CKD, the maintenance dose of digoxin is reduced or switched to digitoxin.

NVL 2023 notes that use of NSAIDs and COX-2 inhibitors is particularly critical in presence of both HF and CKD as they can have adverse effects on each of these.

Monitoring of patients with HF and CKD

NVL 2023 and NICE 2018 both recommend that patients with cHF and CKD are closely monitored (electrolyte balance and kidney function) and dosage of medication adjusted accordingly (increased risk on hyperkalaemia).

NVL 2023 proposes the following timing for monitoring (not formal recommendations):

- before starting therapy and at each change in therapy;
- 1-2 weeks after each dose increase;
- after 3 months and then at least every 6 months (for MRA: every 4 months);
- at each hospitalization

Renal thresholds for drug therapy adjustments when treated with RAAS inhibitors is reported.

Similarly, NHG 2021 recommends more frequent monitoring in case of variation in symptoms, severe renal impairment (eGFR < 30 ml/min/1.73 m2), in frail elderly patients and in patients with past renal function or electrolyte abnormalities with [medication used in heart failure]. Follow-up after 3 and 6 months, and annually thereafter is recommended in patients who have reached the maximum tolerated dose of the medication.

5.4 Morbid obesity

In severe obesity (BMI > 35 kg/m2), NHG 2021 recommends to advise the patient to lose weight and to refer to a dietician if necessary. NHG 2021 also adds that in moderate and severe heart failure, weight loss is not routinely advised because involuntary weight loss and anorexia are common with further progression of heart failure (not formal recommendation).

Due to the obesity paradox, NVL 2023 states that dietary treatment with the aim of weight reduction should not be regularly recommended to patients with chronic heart failure. While not directly formulating formal recommendations, ECS 2021 also considers the obesity paradox but mentioned that other variables may influence this relationship and that the obesity paradox is not observed in patients with diabetes.

5.5 Cachexia /Sarcopenia/ Frailty

AHA/ACC/HFSA 2022 formally states that in adults with HF, screening for depression, social isolation, frailty, and low health literacy as risk factors for poor self-care is reasonable to improve management.

Similarly, NVL 2023 notes that patients with heart failure should be examined for signs of functional decline, especially if there are changes in the course of the disease (e.g. decompensation); geriatric assessment procedures can be used for this purpose and that supportive measures (e.g. physiotherapy, nutritional therapy) should be initiated if there are indications of impending or manifest loss of function.

NHG 2021 also recommends more frequent monitoring in case of variation in symptoms, severe renal impairment (eGFR < 30 ml/min/1.73 m2), in frail elderly patients and in patients with past renal

function or electrolyte abnormalities with [medication used in heart failure]. Follow-up monitoring after 3 and 6 months, and annually thereafter is recommended in patients who have reached the maximum tolerated dose of the medication.

Concerning cachexia:
ESC 2021 further states that non-cardiac causes for cachexia should always be investigated (it is associated with other chronic diseases, such as cancer) (not formal recommendation).

NHG 2021 recommends to pay attention to nutritional status and check whether the patient is getting enough calories in case of unintentional weight loss of > 5% in ≤ 6 months or > 10% in > 6 months; refer to a dietician if necessary. NHG 2021 also specifies that the effect of dietary supplements and appetite-enhancing pharmacotherapy has not been studied.

Concerning sarcopenia:
ESC 2021 specifies that there are no data showing a favourable impact of sarcopenia treatment on outcomes. However, exercise training has favourable effects in patients with HF.

5.6 Severe COPD and pulmonary hypertension

Diagnosis
AHA/ACC/HFSA 2022 recommends that in patients with suspected or new-onset HF, or those presenting with acute decompensated HF, a chest x-ray should be performed to assess heart size and pulmonary congestion and to detect alternative cardiac, pulmonary, and other diseases that may cause or contribute to the patient's symptoms.

NVL 2023 recommends that patients with chronic heart failure and clinical evidence of a pulmonary cause of dyspnea undergo pulmonary function testing. ECS 2021 states that pulmonary function testing with spirometry is recommended as the first diagnostic tool and should be considered in patients with suspected COPD (not formal recommendation).

Management of patients with cHF and COPD
NVL 2023 recommends that patients with cHF and COPD should be treated with cardioselective beta-blockers.

Safety of drugs for patients with HF and COPD
According to ECS 2021, treatment of HF is generally well tolerated in COPD:

- Betablockers can worsen pulmonary function in individual patients but are not contraindicated in either COPD or asthma, as stated in the Global initiative for chronic Obstructive Lung Disease (GOLD) and the Global INitiative for Asthma (GINA), respectively.
- Inhaled corticosteroids and beta-adrenergic agonists do not seem to increase CV events, including HF, in patients at high risk (although not tested in HF patients).

Similarly, NVL 2023 notes in its list of medications causing potential problems an increased heart rate, and arrhythmias with ß2 agonists (LABA/SABA) (e.g. salbutamol, formoterol). But they also report that beta-receptor blocker therapy is usually well tolerated by patients with COPD.

5.7 Atrial fibrillation (interactions between drugs)

Safety of drug used in AF in HF

Treatment with the anti-arrhythmic agents flecainide, encainide, disopyramide, dronedarone, and D-sotalol is not recommended due to safety concerns (ESC 2021). Accordingly, AHA 2022 specifies that in patients with HFrEF, class IC antiarrhythmic medications and dronedarone may increase the risk of mortality. NVL 2023 also reports that Class I (Flecainide, Propafenone) and Class III (dronedarone, sotalol) antiarrhythmics may cause problems due to negative inotropic or proarrhythmic effects.

Diltiazem or verapamil are not recommended in patients with HFrEF (increased risk of HF worsening and HF hospitalization) (NICE 2018-ESC 2021- AHA/ACC/HFSA 2022). Similarly, NHG 2021 recommends to discontinue calcium antagonists with a non-dihydropiridine structure (diltiazem and verapamil (negative inotropic effect) and to check whether substitution with a drug from another group is possible. When substituting, align as much as possible with the drugs recommended in the Heart Failure Medication Step Plan. NVL 2023 also mention the negative inotrope effect of verapamil and diltiazem.

AHA/ACC/HFSA 2022 also specifies that dihydropyridine calcium channel-blocking drugs are not recommended treatment for HF.

Concerning amiodarone, NICE 2018 recommends to:

- Make the decision to prescribe amiodarone in consultation with a specialist.
- Review the need to continue the amiodarone prescription at the 6-monthly clinical review.
- Offer people taking amiodarone liver and thyroid function tests, and a review of side effects, as part of their routine 6-monthly clinical review.

Ivabradine

NVL 2023 recommends that heart rhythm should be monitored regularly during treatment with ivabradine. If there is no stable sinus rhythm, treatment should be discontinued.

6 Heart failure and diabetes - Summary and conclusions from the literature review

6.1 SGLT-2 inhibitors

6.1.1 Dapagliflozin vs placebo

6.1.1.1 HFrEF

6.1.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that diabetes status does not modify the effect of dapagliflozin in comparison to placebo in patients with heart failure with reduced ejection fraction.
In this case, the overall effect applies to patients with and without diabetes.

The DAPA-HF trial (McMurray 2019(18))compared dapagliflozin with placebo for the primary composite outcome of cardiovascular mortality or worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) in patients with HFrEF.
Dapagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

DAPA-HF trial (McMurray 2019(18))with subgroup analysis from Petrie 2020(19)				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death (primary outcome)	0.22	Y	Y	NO
Cardiovascular death	0.70	Y	Y	NO
Cardiovascular death or hospitalization for heart failure (key secondary outcome)	0.83	Y	Y	NO
No. of first and recurrent heart failure hospitalizations and cardiovascular death	0.74	Y	NO	NO
Worsening kidney function	0.86	Y	NO	NO
Death from any cause	0.45	Y	NO	NO
Change in KCCQ total symptom score at 8 mo *The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.*	0.18	Y	NO	NO
SAFETY				

• **Any serious adverse event** • **Discontinuation of study drug due to adverse event** • **Volume depletion** • **Kidney adverse event** • **Fracture** • **Amputation**	No significant p value for interaction	Y	NO	NO

The DEFINE-HF trial (Nassif 2019(20)) compared dapagliflozin with placebo for the primary composite outcome of proportion of patients with ≥5-point increase in HF disease-specific health status on the Kansas City Cardiomyopathy Questionnaire overall summary score, or a ≥20% decrease in NT-proBNP, in patients with HFrEF.
Dapagliflozin had a positive effect on f the primary outcome compared to placebo in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analysis. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in the primary outcome.

DEFINE-HF trial (Nassif 2019(20))				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite: proportion of patients with ≥5-point increase in HF disease-specific health status on the **Kansas City Cardiomyopathy Questionnaire overall summary score**, or a ≥20% decrease in NT-proBNP. **(primary outcome)**	0.304	Y	Y	NO

6.1.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

DAPA-HF trial (McMurray 2019(18))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**

worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death (primary outcome)	**Overall** **HR 0.74 (0.65 to 0.85)** **P<0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 42%) Imprecision: ok
Cardiovascular death	**Overall** **HR 0.82 (0.69 to 0.98)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 42%) Imprecision: ok
Cardiovascular death or hospitalization for heart failure (key secondary outcome)	**Overall** **HR 0.75 (0.65 to 0.85)** **P<0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 42%) Imprecision: ok
No. of first and recurrent heart failure hospitalizations and cardiovascular death	**Overall** **RR 0.75 (0.65 to 0.88)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 42%) Imprecision: ok
Worsening kidney function	Overall HR 0.71 (0.44 to 1.16)	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 (diabetes population 42%) Imprecision: -1
Death from any cause	**Overall** **HR 0.83 (0.71 to 0.97)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 42%) Imprecision: ok
Change in KCCQ total symptom score at 8 mo *The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.*	Overall **RR 1.18 (1.11 to 1.26)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 42%) Imprecision: ok
• **Any serious adverse event** • **Discontinuation of study drug due to adverse event** • **Volume depletion**	Post hoc analysis by subgroup No significant p value for interaction	Unable to assess

• **Kidney adverse event** • **Fracture** • **Amputation**		

DEFINE-HF trial (Nassif 2019(20))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite: proportion of patients with ≥5-point increase in HF disease-specific health status on the **Kansas City Cardiomyopathy Questionnaire overall summary score**, or a ≥20% decrease in NT-proBNP. **(primary outcome)**	**Overall** **adjusted OR 1.8, 95% CI 1.03–3.06** **p<0.039** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 62%) Imprecision: ok

6.1.1.2 HFpEF

6.1.1.2.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that diabetes status does not modify the effect of dapagliflozin in comparison to placebo in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without diabetes.

The DELIVER trial (Solomon 2022(21)) compared dapagliflozin with placebo for the primary composite outcome of worsening heart failure, which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure, or cardiovascular death in patients with HFpEF.
Dapagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

DELIVER trial (Solomon 2022(21)) with subgroup analysis from Inzucchi 2022(22);				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05

Composite of worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	0.82	Y	Y	NO
CV death	0.63	Y	NO	NO
Heart failure event (hospitalization or urgent visit)	0.74	Y	NO	NO
Heart failure hospitalization	0.72	Y	NO	NO
Urgent heart failure visit	0.38	Y	NO	NO
Composite of cardiovascular death and all heart failure events (including recurrent)	0.58	Y	NO	NO
Death from any cause	0.14	Y	NO	NO

6.1.1.2.2 How much confidence do we have that the overall results are applicable in this specific population?

DELIVER trial (Solomon 2022(21))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite of worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	**Overall** **HR 0.82 (0.73-0.92)** **p<0.001** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok
CV death	Overall HR 0.88 (0.74 to 1.05)	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok
Heart failure event (hospitalization or urgent visit)	**Overall** **HR 0.79 (0.73-0.91)**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok
Heart failure hospitalization	**Overall**	⨁⨁⨁⨀ **MODERATE** Study quality: ok

	HR 0.77 (0.67-0.89	Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok
Urgent heart failure visit	Overall HR 0.76 (0.55 to 1.07)	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok
Composite of cardiovascular death and all heart failure events (including recurrent)	**Overall** **RR 0.77 (0.67 to 0.89)**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok
Death from any cause	Overall HR 0.94 (0.83 to 1.07)	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok

6.1.2 Empagliflozin vs placebo

6.1.2.1 HFrEF

6.1.2.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that diabetes status does not modify the effect of empagliflozin in comparison to placebo in patients with heart failure with reduced ejection fraction.
In this case, the overall effect applies to patients with and without diabetes.

The EMPEROR-reduced trial (Packer 2020(23)) compared empagliflozin with placebo for the primary composite outcome of cardiovascular mortality or heart failure hospitalization (HHF) in patients with HFrEF.
Empagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

EMPEROR-reduced Packer 2020(23); with subgroup analysis from Anker 2021b(24)				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05

Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	0.57	**Y**	**Y**	**NO**
First and recurrent HHF	0.44	**Y**	**Y**	**NO**
Renal slope (eGFR mean slope change/year)	0.15	**Y**	**Y**	**NO**
Composite renal endpoint	0.65	**Y**	**NO**	**NO**
First HHF	0.66	**Y**	**Y**	**NO**
Time to CV death	0.98	**Y**	**Y**	**NO**
Changes in KCCQ clinical summary score at week 52	0.30	**Y**	**NO**	**NO**

The EMPERIAL-reduced trial (Abraham 2021(25)) compared empagliflozin with placebo for the primary outcome of 6-minute walk test distance change to week 12 in patients with heart failure with reduced ejection fraction.
There was no difference in the risk of the primary outcome of 6-minute walk test distance change to week 12 compared to placebo in the overall population
Empagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in the primary outcome.

EMPERIAL Reduced (Abraham 2021(25))				
Outcome	Result (95%CI)	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
6-minute walk test distance change to week 12 **(primary outcome)**	**Interaction p value**: not performed	YES	YES	NO

6.1.2.1.2 How much confidence do we have that the overall results are applicable in this specific population?

EMPEROR-reduced Packer 2020(23)

Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall **HR 0.75 (0.65-0.86)** **p<0.001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 50%) Imprecision: ok
First and recurrent HHF	**Overall: HR 0.70 (0.58, 0.85)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 50%) Imprecision: ok
Renal slope (eGFR mean slope change/year)	**Overall: Difference 1.73 (1.10, 2.37)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 50%) Imprecision: ok
Composite renal endpoint	**Overall: HR 0.50 (0.32-0.77)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 50%) Imprecision: ok
First HHF	**Overall: HR 0.69 (0.59, 0.81)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 50%) Imprecision: ok
Time to CV death	Overall: HR 0.92 (0.75, 1.12)	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 50%) Imprecision: ok
Changes in KCCQ clinical summary score at week 52	**Overall:** **Difference 1.75 (0.5, 3.0)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 50%) Imprecision: ok

EMPERIAL Reduced (Abraham 2021(25))		
Outcome	Result (95%CI)	**Quality of the evidence (GRADE)**
6-minute walk test distance change to week 12 **(primary outcome)**	Overall Difference -4.0 m (-16.0, 6.0) p<0.42 NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 59%) Imprecision: ok

6.1.2.2 HFpEF

6.1.2.2.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that diabetes status does not modify the effect of empagliflozin in comparison to placebo in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without diabetes.

The EMPEROR-preserved trial (Anker 2021a(26)) compared empagliflozin with placebo for the primary composite outcome of cardiovascular mortality or heart failure hospitalization (HHF) in patients with HFpEF.
Empagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

EMPEROR-preserved (Anker 2021a(26)); with subgroup analyses from Filippatos 2022(27); Siddiqi 2023(28)				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite outcome cardiovascular mortality or HF hospitalization **(primary outcome)**	0.92	**Y**	**Y**	**NO**
First and recurrent HFF	0.97	**Y**	**NO**	**NO**
Time to first HHF	0.66	**Y**	**NO**	**NO**
Time to CV death	0.32	**Y**	**NO**	**NO**
Time to all-cause mortality	0.43	**Y**	**NO**	**NO**
Composite renal end point	0.62	**Y**	**NO**	**NO**
Kansas City Cardiomyopathy Questionnaire (KCCQ) changes in clinical summary score at 52 weeks	0.51	**Y**	**NO**	**NO**

The EMPERIAL-preserved trial (Abraham 2021(25)) compared empagliflozin with placebo for the primary outcome of 6-minute walk test distance change to week 12 in patients with heart failure with preserved ejection fraction.
Empagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.

The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in the primary outcome.

EMPERIAL Preserved (Abraham 2021(25))				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
6-minute walk test distance change to week 12 **(primary outcome)**	Interaction p value: not performed	YES	YES	NO

6.1.2.2.2 How much confidence do we have that the overall results are applicable in this specific population?

EMPEROR-preserved (Anker 2021a(26))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall **HR 0.79 (0.69-0.90)** **<0.001** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 49%) Imprecision: ok
First and recurrent HFF	Overall **0.73 (0.61, 0.88)** **<0.001** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 49%) Imprecision: ok
Time to first HHF	Overall **HR 0.71 (0.60, 0.83)**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 49%) Imprecision: ok
Time to CV death	Overall HR 0.91 (0.76, 1.09)	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 49%) Imprecision: ok
Time to all-cause mortality	Overall	⨁⨁⨁⨀ **MODERATE**

	HR 1.00 (0.87, 1.15)	Study quality: ok Consistency: NA Directness: -1 (diabetes population 49%) Imprecision: ok
Composite renal end point	Overall HR 0.95 (0.73,1.24)	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 (diabetes population 49%) Imprecision: -1
Kansas City Cardiomyopathy Questionnaire (KCCQ) changes in clinical summary score at 52 weeks	Overall 4.51±0.31 vs 3.18±0.31 Difference 1.32 (0.45-2.19)	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 49%) Imprecision: ok

EMPERIAL Preserved (Abraham 2021(25))		
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	**Quality of the evidence (GRADE)**
6-minute walk test distance change to week 12 **(primary outcome)**	Overall Difference -4.0 m (-16.0, 6.0) p<0.42 NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 50%) Imprecision: ok

6.2 MRA

6.2.1 Eplerenone vs placebo

6.2.1.1 HFrEF

6.2.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that diabetes status does not modify the effect of eplerenone in comparison to placebo in patients with heart failure with reduced ejection fraction.
In this case, the overall effect applies to patients with and without diabetes.

The EMPHASIS-HF trial (Zannad 2011(29)) compared eplerenone with placebo for the primary composite outcome of death from cardiovascular causes or a first hospitalization for heart failure in patients with HFrEF.
Eplerenone reduced the risk of the primary outcome compared to placebo in the overall population. The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

EMPHASIS-HF trial (Zannad 2011(29)) with subgroup analysis from Ferreira 2021(30))				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
death from cardiovascular causes or hospitalization for heart failure (primary outcome)	0.09	Y	Y	NO
HF hospitalization	0.27	Y	NO	NO
CV Death	0.80	Y	NO	NO
All-cause death or all-cause hospitalization	0.37	Y	NO	NO
All-cause hospitalization	0.72	Y	NO	NO
All-cause death	0.91	Y	NO	NO
SAFETY				
Hyperkalemia	0.32		NO	NO
Hypokalemia	0.69		NO	NO
Renal failure	0.67		NO	NO
Hypotension	0.56		NO	NO

The J-EMPHASIS trial (Tsutsui 2017(31)) compared eplerenone with placebo for the primary composite outcome of death from cardiovascular causes or hospitalization for heart failure in Japanese patients with HFrEF.

To demonstrate efficacy, the consistency of results with the EMPHASIS-HF study was predefined as a point estimate of the hazard ratio <1 in the primary endpoint. This was demonstrated in the overall population of J-EMPAHSIS.

The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in a subgroup analysis. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in the primary outcome.

J-EMPHASIS trial (Tsutsui 2017(31))				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
death from cardiovascular causes or hospitalization for heart failure **(primary outcome)**	0.64	Y	Y	NO

The EPHESUS trial (Pitt 2003(32)) compared eplerenone with placebo for the co-primary composite outcomes of death from any cause and death from cardiovascular causes or hospitalization for cardiovascular events (including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia) in patients with HFrEF, 3 to 14 days after acute myocardial infarction. Eplerenone reduced the risk of the co-primary outcomes compared to placebo in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

EPHESUS trial (Pitt 2003(32)				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
death from any cause **(primary outcome)**	0.35	Y	Y	NO
Death from cardiovascular causes or hospitalization for cardiovascular events **(primary outcome)**	0.59	Y	Y	NO

6.2.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

EMPHASIS-HF trial (Zannad 2011(29))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
death from cardiovascular causes or hospitalization for heart failure (primary outcome)	**Overall** **adjusted HR 0.63 (0.54–0.74) <** **p<0.001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 31%) Imprecision: ok
HF hospitalization	**Overall** **HR 0.58 (0.48 to 0.71)** **P<0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 31%) Imprecision: ok
CV Death	**Overall** **HR 0.75 (0.6 to 0.93)** **P0.01**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 31%) Imprecision: ok
All-cause death or all-cause hospitalization	**Overall** **HR 0. 0.76 (0.67 to 0.86)** **p<0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 31%) Imprecision: ok
All-cause hospitalization	**Overall** **HR 0.77 (0.68 to 0.88)** **p<0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 31%) Imprecision: ok
All-cause death	**Overall** **HR 0.76 (0.62 to 0.92)** **P 0.007**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 31%) Imprecision: ok
Hyperkalemia	**Overall** **Placebo: 50/1373 (3.7%)** **Eplerenone: 109/1364 (8.0%)** **P <0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 31%) Imprecision: ok

Hypokalemia	**Overall** **Placebo: 31/1373 (2.3%)** **Eplerenone: 16/1364 (1.2%)** **P 0.032**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 31%) Imprecision: ok
Renal failure	Overall Placebo: 41/1373 (3.0%) Eplerenone: 39/1364 (2.0%) P 0.84	Unable to assess
Hypotension	Overall Placebo: 37/1373 (2.7%) Eplerenone: 46/1364 (3.4%) P 0.30	Unable to assess

J-EMPHASIS trial (Tsutsui 2017(31))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
death from cardiovascular causes or hospitalization for heart failure **(primary outcome)**	Overall HR 0.85 (0.53 to 1.36) P 0.50	⊕⊖⊖⊖ **VERY LOW** Study quality: ok Consistency: NA Directness: -2 (diabetes population 40%; Japanese population only) Imprecision: -1

EPHESUS trial (Pitt 2003(32)		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
death from any cause **(primary outcome)**	**Overall** **RR 0.85 (0.75–0.96)** **P 0.008**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 32%) Imprecision: ok
Death from cardiovascular causes or hospitalization for cardiovascular events **(primary outcome)**	**Overall** **RR 0.87 (0.79–0.95)** **P 0.002**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 32%) Imprecision: ok

6.2.2 Spironolactone vs placebo

6.2.2.1 HFpEF

6.2.2.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that diabetes status does not modify the effect of spironolactone in comparison to placebo in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without diabetes.

The TOPCAT trial (Pitt 2014(33)) compared spironolactone with placebo for the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure in patients with HFpEF.
There was no difference in risk of the primary outcome with spironolactone compared to placebo in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analysis. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in the primary outcome.

TOPCAT trial (Pitt 2014(33))				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **(primary outcome)**	0.82	Y	Y	NO

6.2.2.1.2 How much confidence do we have that the overall results are applicable in this specific population?

TOPCAT trial (Pitt 2014(33))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure	Overall HR 0.89 (0.77-1.04) NS	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (diabetes population 10%)

(primary outcome)		Imprecision: ok

6.3 ARNI

6.3.1 Sacubitril/valsartan vs enalapril

6.3.1.1 HFrEF

6.3.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that diabetes status does not modify the effect of sacubitril/valsartan in comparison to enalapril in patients with heart failure with reduced ejection fraction.
In this case, the overall effect applies to patients with and without diabetes.

The PARADIGM-HF trial (McMurray 2014(14)) compared sacubitril/valsartan with enalapril for the primary composite outcome of time to CV death or first hospitalization for heart failure in patients with HFrEF.
Sacubitril/valsartan reduced the risk of the primary outcome compared to enalapril in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect in prespecified analysis** of primary outcome.
The test for subgroup differences was **statistically significant** in one of the **exploratory outcomes** but the analysis for **the effect of diabetes was not prespecified**. As prespecification of a subgroup analysis is a critical attribute to be considered plausible, **further research is necessary before considering taking clinical action on the basis of this result.**

PARADIGM-HF trial (McMurray 2014(14))				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite of cardiovascular death or first hospital admission for heart failure (primary outcome)	0.40	Y	Y	NO
Cardiovascular death (component outcome)	0.052	Y	Y	NO

PARADIGM-HF trial (McMurray 2014(14)) with subgroup analysis from Packer 2018 (34)

Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
eGFR decline (mL/min per 1·73m² per year) (expl. outcome)	**0.038**	Y	NO	**YES**

PARADIGM-HF trial (McMurray 2014(14)) with subgroup analysis from Seferovic 2017 (35)				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Cardiovascular death (analysis restricted to the 12 first months)	Not reported	Y	NO	N.R. (NO in primary study)
HbA1c concentration (%) 3 years (expl. outcome)	Not reported	Y	NO	N.R
Incident diabetes	N.A. (only for the no-diabetes group)	Y	NO	N.A.
New initiation of insulin therapy (Incidence rate (per 100 person-years))	N.A. (only for the diabetes group)	Y	NO	N.A.
BMI (kg/m2)	Not reported	Y	NO	N.R

6.3.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

PARADIGM-HF trial (McMurray 2014(14))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite of cardiovascular death or first hospital admission for heart failure (primary outcome)	Overall **HR: 0·80 (0·73–0·87)** **P < 0·001**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok
Cardiovascular death (component outcome)	Overall **HR : 0·80 (0·71–0·89)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA

	P < 0·001	Directness: -1 (diabetes population 45%) Imprecision: ok
eGFR decline (mL/min per 1·73m² per year) (expl. outcome)	Overall **MD: 0·4 (0·3 to 0·6)** **P < 0·0001**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok
HbA1c concentration (%) 3 years (expl. outcome)	Overall MD: -0.01 (-0.04 to 0.01) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok

6.3.2 Sacubitril/valsartan vs valsartan

6.3.2.1 HFpEF

6.3.2.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that diabetes status does not modify the effect of sacubitril/valsartan in comparison to valsartan in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without diabetes.

The PARAGON-HF trial (Solomon 2019(15)) compared sacubitril/valsartan with valsartan for the primary composite outcome of time to CV death or total (first and recurrent) hospitalization for heart failure in patients with HFpEF.

The primary composite outcome **did not differ significantly** between **sacubitril/valsartan** and valsartan in the overall population. Because this difference did not meet the predetermined level of statistical significance, **subsequent analyses are to be considered exploratory.**
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect in prespecified analysis** of primary outcome.

PARAGON-HF trial (Solomon 2019(15))				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite of total hospitalizations for heart failure and death from cardiovascular causes. (primary outcome)	NS	Y	Y	NO

6.3.2.1.2 How much confidence do we have that the overall results are applicable in this specific population?

PARAGON-HF trial (Solomon 2019(15))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite of total hospitalizations for heart failure and death from cardiovascular causes. (primary outcome)	Overall RR: 0.87 (0.75-1.01) P =0.06 NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (diabetes population 35%) Imprecision: ok

6.3.3 Sacubitril/valsartan vs standard therapy

6.3.3.1 HFpEF

6.3.3.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that diabetes status does not modify the effect of sacubitril/valsartan in comparison to standard therapy in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without diabetes.

The PARALLAX trial (Pieske 2021(36)) compared sacubitril/valsartan with "standard medical therapy" (either valsartan, enalapril or placebo depending on what medication patients were taking prior to enrolling) for the primary composite outcome change in the 6-minute walk distance from baseline to week 24 in patients with HFpEF.
There was no difference in the primary outcome with sacubitril/valsartan compared to placebo in the overall population.
The consistency of effects in diabetes patients versus non-diabetic patients was evaluated in subgroup analysis. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in the primary outcome.

TOPCAT trial (Pieske 2021(36))				
Outcome	**Interaction p-value** of SUBGROUP Diabetes vs no diabetes	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05

composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **(primary outcome)**	0.82	Y	Y	NO

6.3.3.1.2 How much confidence do we have that the overall results are applicable in this specific population?

TOPCAT trial (Pitt 2014(33))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
change in the 6-minute walk distance from baseline to week 24 (in the subgroup of patients with a baseline ability of walk between 100 m and 450 m) *An increase by 30 m was considered as a minimal clinically important difference* **(primary outcome)**	Overall Adj. MD -2.50 m (-8.53 to 3.53) NS	⨁⨁⊖⊖ **LOW** Study quality: -1 (primary analysis in (prespecified) subgroup of total population) Consistency: NA Directness: -1 (diabetes population 45%) Imprecision: ok

7 Heart failure and chronic kidney disease- Summary and conclusions from the literature review

7.1 SGLT-2 inhibitors

7.1.1 Dapagliflozin vs placebo

7.1.1.1 HFrEF

7.1.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that chronic kidney disease(CKD) status does not modify the effect of dapagliflozin in comparison to placebo in patients with heart failure with reduced ejection fraction. In this case, the overall effect applies to patients with and without CKD.

The DAPA-HF trial (McMurray 2019(18))compared dapagliflozin with placebo for the primary composite outcome of cardiovascular mortality or worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) in patients with HFrEF.
Dapagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in CKD patients versus non-CKD patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

DAPA-HF trial (McMurray 2019(18))with subgroup analysis from Jhund 2021(37)				
Outcome	**Interaction p-value** of SUBGROUP CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	0.54	Y	Y	NO
Cardiovascular death	0.44	Y	Y	NO
Cardiovascular death or hospitalization for heart failure **(key secondary outcome)**	0.50	Y	Y	NO
Worsening kidney function (≥50% sustained decline eGFR or end-stage renal disease or renal death)	0.19	Y	NO	NO
Death from any cause	0.80	Y	NO	NO
Change in KCCQ total symptom score at 8 mo *The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.*	0.52	Y	NO	NO

7.1.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

DAPA-HF trial (McMurray 2019(18))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	**Overall** **HR 0.74 (0.65 to 0.85)** **P<0.001**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 41%) Imprecision: ok
Cardiovascular death	**Overall** **HR 0.82 (0.69 to 0.98)** pNA	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 41%) Imprecision: ok
Cardiovascular death or hospitalization for heart failure **(key secondary outcome)**	**Overall** **HR 0.75 (0.65 to 0.85)** **P<0.001**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 41%) Imprecision: ok
Worsening kidney function (≥50% sustained decline eGFR or end-stage renal disease or renal death)	Overall HR 0.71 (0.44 to 1.16) P 0.17	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -1 (CKD population 41%) Imprecision: -1
Death from any cause	Overall **HR 0.83 (0.71 to 0.97)** **P NA**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 41%) Imprecision: ok
Change in KCCQ total symptom score at 8 mo *The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.*	Overall **RR 1.18 (1.11 to 1.26)** **P<0.001**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 41%) Imprecision: ok

7.1.1.2 HFpEF

7.1.1.2.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that CKD status does not modify the effect of dapagliflozin in comparison to placebo in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without CKD.

The DELIVER trial (Solomon 2022(21)) compared dapagliflozin with placebo for the primary composite outcome of worsening heart failure, which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure, or cardiovascular death in patients with HFpEF.
Dapagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in CKD patients versus non-CKD patients, and in 3 different eGFR categories (eGFR ≥60; 45 to <60 mL; and <45 mL/min/1.73 m²), was evaluated in subgroup analyses.
The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified outcomes and a **statistically significant subgroup effect in one non-prespecified** outcome (heart failure event). **As it was non-prespecified, this effect can only be considered as exploratory and further research is necessary before considering taking clinical action on the basis of this result.**

DELIVER trial (Solomon 2022(21)) with subgroup analysis from Mc Causland 2023(38)				
Outcome	**Interaction p-value** of SUBGROUPS eGFR ≥60; 45 to <60 mL; and <45 mL/min/1.73 m²	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death (primary outcome)	0.16	Y	Y	NO
CV death	0.96	Y	NO	NO
Heart failure event (hospitalization or urgent visit)	0.04	Y	NO	YES
Heart failure hospitalization	0.05	Y	NO	NO
Worsening kidney function Mean decline in eGFR	0.29	Y	NO	NO
Kidney composite end point (≥50% decline in eGFR, end-stage kidney disease or death from kidney causes)	0.34	Y	NO	NO

(**post hoc definition)**				

7.1.1.2.2 How much confidence do we have that the overall results are applicable in this specific population?

DELIVER trial (Solomon 2022(21))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	**Overall** **HR 0.82 (0.73-0.92)** **p<0.001** **SS**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 49%) Imprecision: ok
CV death	Overall HR 0.88 (0.74 to 1.05) P NA	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 49%) Imprecision: ok
Heart failure event (hospitalization or urgent visit)	**Overall** **HR 0.79 (0.73-0.91)** P NA	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 49%) Imprecision: ok
Heart failure hospitalization	**Overall** **HR 0.77 (0.67-0.89** P NA	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 49%) Imprecision: ok
Worsening kidney function Mean decline in eGFR	**Overall** **MD: 1.4 (95% CI, 1.0-1.8) mL/min/1.73 m² per year** **P<0.001**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 49%) Imprecision: ok
Kidney composite end point (≥50% decline in eGFR, end-stage kidney disease or death from kidney causes) (**post hoc definition)**	Overall HR 1.08 (0.79-1.49)	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -1 (CKD population 49%) Imprecision: -1

7.1.2 Empagliflozin vs placebo

7.1.2.1 HFrEF

7.1.2.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that CKD status does not modify the effect of empagliflozin in comparison to placebo in patients with heart failure with reduced ejection fraction.
In this case, the overall effect applies to patients with and without CKD.

There may be a difference in the effect of empagliflozin on the eGFR slope (rate of decline) in CKD patients versus non-CKD patients. In CKD patients the slowing of the slope may be less pronounced than in non-CKD patients.
The difference in effect probably did not occur by chance, but the estimated subgroup effect warrants **LOW confidence** because other criteria were not met.
The clinical importance of this effect is likely limited.

The EMPEROR-reduced trial (Packer 2020(23)) compared empagliflozin with placebo for the primary composite outcome of cardiovascular mortality or heart failure hospitalization (HHF) in patients with HFrEF.
Empagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in CKD patients versus non-CKD patients; and in five eGFR-categories (<30, 30–44, 45–59, 60–89, and ≥90 ml/min/1.73 m²) was evaluated in subgroup analyses.
The test for subgroup differences indicates that there is **a statistically significant subgroup effect** in one **prespecified** outcome (renal slope).

EMPEROR-reduced Packer 2020(23); with subgroup analysis from Zannad 2021(39)				
Outcome	**Interaction p-value** of SUBGROUP	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	CKD vs no CKD 0.63 5 eGFR categories 0.12	**Y**	**Y**	**NO**
First and recurrent HHF	CKD vs no CKD 0.78 5 eGFR categories 0.06	**Y**	**Y**	**NO**

Renal slope (eGFR mean slope change/year)	**CKD vs no CKD** **0.045** **5 eGFR categories** **0.033**	**Y**	**Y**	**Y**
Composite renal endpoint (the need for chronic dialysis or renal transplant or a ≥40% sustained reduction in eGFR or a sustained eGFR <15ml/min/1.73 m2 (if baseline eGFR was ≥30 ml/min/1.73 m2) or <10 ml/min/1.73 m2 (if baseline eGFR was <30 ml/min/1.73 m2)	CKD vs no CKD 0.78 5 eGFR categories 0.74	**Y**	**Y**	**NO**

7.1.2.1.2 How credible is the observed subgroup effect?

Full assessment of the credibility of the subgroup effect

Ten criteria used to assess credibility of subgroup effect (Sun 2012(11))	
Design	
Was the subgroup variable a baseline characteristic?	Yes
Was the subgroup variable a stratification factor at randomisation?	Yes, Randomization was stratified according to geographical region (North America, Latin America, Europe, Asia, or other), diabetes status at screening, and eGFR at screening (<60 or ≥60 ml/min/1.73 m2)
Was the subgroup hypothesis specified a priori?	Yes
Was the subgroup analysis one of a small number of subgroup hypotheses tested (≤5)?	**No; 20 subgroups planned for 5 outcomes**
Analysis	
Was the test of interaction significant (interaction P <0.05)?	Yes
Was the significant interaction effect independent, if there were multiple significant interactions?	NA
Context	
Was the direction of subgroup effect correctly prespecified?	**No; not prespecified**

Was the subgroup effect consistent with evidence from previous related studies?	NA
Was the subgroup effect consistent across related outcomes?	**No, composite renal endpoint does not show subgroup interaction effect**
Was there any indirect evidence to support the apparent subgroup effect—for example, biological rationale, laboratory tests, animal studies?	Yes, explanation from authors: "these analyses are model-dependent and are based on absolute differences. Given the lower baseline values for eGFR in patients with CKD, the magnitude of benefit on eGFR slope with empagliflozin was proportionally similar in patients with and without CKD"

7.1.2.1.3 How much confidence do we have that the overall results are applicable in this specific population?

EMPEROR-reduced Packer 2020(23)		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall **HR 0.75 (0.65-0.86)** **p<0.001** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53%) Imprecision: ok
First and recurrent HHF	**Overall: HR 0.70 (0.58, 0.85)** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53%) Imprecision: ok
Renal slope (eGFR mean slope change/year)	**Overall: Difference 1.73 (1.10, 2.37)** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53%) Imprecision: ok
Composite renal endpoint	**Overall: HR 0.50 (0.32-0.77)**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53%) Imprecision: ok

7.1.2.2 HFpEF

7.1.2.2.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that CKD status does not modify the effect of empagliflozin in comparison to placebo in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without CKD.

The EMPEROR-preserved trial (Anker 2021a(26)) compared empagliflozin with placebo for the primary composite outcome of cardiovascular mortality or heart failure hospitalization (HHF) in patients with HFpEF.
Empagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in CKD patients versus non-CKD patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

EMPEROR-preserved (Anker 2021a(26)); with subgroup analyses from Sharma 2023(40); Siddiqi 2023(28)				
Outcome	**Interaction p-value** of SUBGROUP CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite outcome cardiovascular mortality or HF hospitalization **(primary outcome)**	0.67	**Y**	**Y**	**NO**
First and recurrent HFF	0.17	**Y**	**NO**	**NO**
Time to first HHF	0.79	**Y**	**NO**	**NO**
Time to CV death	0.17	**Y**	**NO**	**NO**
Time to all-cause mortality	0.51	**Y**	**NO**	**NO**
All-cause hospitalisation	0.67	**Y**	**NO**	**NO**
Slope of change in eGFR ml/min/1.73m² per year	0.97		**NO**	**NO**
Composite renal end point*	0.86		**NO**	**NO**
Acute kidney injury	0.67		**NO**	**NO**
Progression to macroalbuminuria	0.77		**NO**	**NO**
Kansas City Cardiomyopathy Questionnaire (KCCQ) changes in clinical summary score at 52 weeks	0.51	**Y**	**NO**	**NO**

7.1.2.2.2 How much confidence do we have that the overall results are applicable in this specific population?

EMPEROR-preserved (Anker 2021a(26))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite outcome cardiovascular mortality or HF hospitalization **(primary outcome)**	**Overall** **HR 0.79 (0.69-0.90)** **<0.001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: ok
First and recurrent HFF	**Overall** **HR 0.73 (0.61, 0.88)** **<0.001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: ok
Time to first HHF	**Overall** **HR 0.71 (0.60, 0.83)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: ok
Time to CV death	Overall HR 0.91 (0.76, 1.09)	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: ok
Time to all-cause mortality	Overall HR 1.00 (0.87, 1.15)	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: ok
All-cause hospitalisation	**Overall** **HR 0.92 (0.85, 0.99)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: ok
Slope of change in eGFR ml/min/1.73m² per year	**Overall** **Difference 2.4 (1.6-3.2)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%)

		Imprecision: ok
Composite renal end point*	Overall HR 0.95 (0.73 to 1.24)	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: -1
Acute kidney injury	**Overall** **HR 0.73 (0.56 – 0.95)**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: ok
Progression to macroalbuminuria	**Overall** **HR 0.82 (0.68, 0.98)**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: ok
Kansas City Cardiomyopathy Questionnaire (KCCQ) changes in clinical summary score at 52 weeks	**Overall** **Difference 1.32 (0.45-2.19)**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 53.4%) Imprecision: ok

7.2 MRA

7.2.1 Eplerenone vs placebo

7.2.1.1 HFrEF

7.2.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that CKD status does not modify the effect of eplerenone in comparison to placebo in patients with heart failure with reduced ejection fraction.
In this case, the overall effect applies to patients with and without CKD.

The EMPHASIS-HF trial (Zannad 2011(29)) compared eplerenone with placebo for the primary composite outcome of death from cardiovascular causes or a first hospitalization for heart failure in patients with HFrEF.
Eplerenone reduced the risk of the primary outcome compared to placebo in the overall population. The consistency of effects in CKD patients versus non-CKD patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

EMPHASIS-HF trial (Zannad 2011(29)) with subgroup analysis from Ferreira 2019(41)				
Outcome	**Interaction p-value** of CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
death from cardiovascular causes or hospitalization for heart failure (primary outcome)	SUBGROUP eGFR≥ vs <60 mL/min/1.73m Interaction p value 0.50	Y	Y	NO
	SUBGROUP eGFR≥ vs <50 mL/min/1.73m Interaction p value 0.89	Y	NO	NO

The J-EMPHASIS trial (Tsutsui 2017(31)) compared eplerenone with placebo for the primary composite outcome of death from cardiovascular causes or hospitalization for heart failure in Japanese patients with HFrEF.
To demonstrate efficacy, the consistency of results with the EMPHASIS-HF study was predefined as a point estimate of the hazard ratio <1 in the primary endpoint. This was demonstrated in the overall population of J-EMPAHSIS.
The consistency of effects in CKD patients versus non-diabetic patients was evaluated in a subgroup analysis. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in the primary outcome.

J-EMPHASIS trial (Tsutsui 2017(31))				
Outcome	**Interaction p-value** of SUBGROUP CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
death from cardiovascular causes or hospitalization for heart failure (primary outcome)	0.39	Y	Y	NO

7.2.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

EMPHASIS-HF trial (Zannad 2011(29))

Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
death from cardiovascular causes or hospitalization for heart failure (primary outcome)	**Overall** **adjusted HR 0.63 (0.54–0.74) <** **p<0.001** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 33%) Imprecision: ok

J-EMPHASIS trial (Tsutsui 2017(31))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
death from cardiovascular causes or hospitalization for heart failure **(primary outcome)**	Overall HR 0.85 (0.53 to 1.36) P 0.50	⨁⊖⊖⊖ **VERY LOW** Study quality: ok Consistency: NA Directness: -2 (CKD population 60.2%; Japanese population only) Imprecision: -1

7.2.2 Spironolactone vs placebo

7.2.2.1 HFrEF

7.2.2.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that CKD status does not modify the effect of spironolactone in comparison to placebo in patients with heart failure with reduced ejection fraction.
In this case, the overall effect applies to patients with and without CKD.

The RALES trial (Pitt 1999 (42)) compared spironolactone with placebo for the primary composite outcome of all-cause mortality in patients with HFrEF.
Spironolactone reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in CKD patients versus non-CKD patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.

RALES trial (Pitt 1999 (42)) with subgroup analysis from Vardeny 2012(43)				
Outcome	**Interaction p-value** of CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05

All-cause mortality (primary outcome)	Interaction p value: not reported Described narratively as being consistent with overall results	Y	Y	NO
Death or HF hospital stay	Interaction p value: not reported Described narratively as being consistent with overall results	Y	NO	NO

7.2.2.1.2 How much confidence do we have that the overall results are applicable in this specific population?

RALES trial (Pitt 1999 (42))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
All-cause mortality (primary outcome)	**Overall** **RR 0.70 (95% CI 0.60 to 0.82)** **P <0.001** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 47.8%) Imprecision: ok
Death or HF hospital stay	**Overall** **RR 0.68 (95% CI 0.59 to 0.78)** **P <0.001** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 47.8%) Imprecision: ok

7.2.2.2 HFpEF

7.2.2.2.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that CKD status does not modify the effect of spironolactone in comparison to placebo in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without CKD.

The TOPCAT trial (Pitt 2014(33)) compared spironolactone with placebo for the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure in patients with HFpEF.
There was no difference in risk of the primary outcome with spironolactone compared to placebo in the overall population.
The consistency of effects in CKD patients versus non-CKD patients was evaluated in subgroup analysis. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in the primary outcome.

TOPCAT trial (Pitt 2014(33))				
Outcome	**Interaction p-value** of SUBGROUP CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **(primary outcome)**	0.34	Y	Y	NO

Post hoc analyses identified important regional differences (patient characteristics, outcomes etc.) between patients randomized from the Americas cohort and from Russia/Georgia.
TOPCAT Americas (Pfeffer 2014(44)) was a post hoc analysis of the TOPCAT trial using only data from the Americas (United States, Canada, Brazil, and Argentina); excluding the participants from Russia/Georgia.
In this analysis, spironolactone reduced the risk of the primary outcome with spironolactone compared to placebo.

The consistency of effects in 3 eGFR-categories (eGFR ≥60; 45 to <60 mL; and <45 mL/min/1.73 m²), was evaluated in a subgroup analysis. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in the primary outcome.

TOPCAT Americas (Pfeffer 2014(44)); with subgroup analysis from Beldhuis 2019(45)				
Outcome	**Interaction p-value** of eGFR ≥60; 45 to <60 mL; and <45 mL/min/1.73 m²	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure	0.13	Y	NO	NO

(primary outcome)				

7.2.2.2.2 How much confidence do we have that the overall results are applicable in this specific population?

TOPCAT trial (Pitt 2014(33))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **(primary outcome)**	Overall HR 0.89 (0.77-1.04) NS	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (CKD population 9.3%) Imprecision: ok

TOPCAT Americas (Pfeffer 2014(44));		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **(primary outcome)**	**Overall** **HR 0.82(0.69–0.98)** **p 0.026**	⨁⨀⨀⨀ **VERY LOW** Study quality: -2 (subgroup analysis) Consistency: NA Directness: -1 (CKD population 53%) Imprecision: ok

7.3 Angiotensin Receptor-Neprilysin Inhibitor (ARNI)

7.3.1 Sacubitril/valsartan vs enalapril

7.3.1.1 HFrEF

7.3.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that CKD status does not modify the effect of sacubitril/valsartan in comparison to enalapril in patients with heart failure with reduced ejection fraction.

In this case, the overall effect applies to patients with and without CKD.

The PARADIGM-HF trial (McMurray 2014(14)) compared sacubitril/valsartan with enalapril for the primary composite outcome of time to CV death or first hospitalization for heart failure in patients with HFrEF.
Sacubitril/valsartan reduced the risk of the primary outcome compared to enalapril in the overall population.
The consistency of effects in CKD patients versus non-CKD patients and in for eGFR-categories (<45, 45–60, 61–90, and > 90 ml/min/1.73 m²) was evaluated in subgroup analyses. was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect in prespecified analysis** of primary outcome **and in non-prespecified analysis.**

PARADIGM-HF trial (McMurray 2014(14))				
Outcome	**Interaction p-value** of SUBGROUP CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite of cardiovascular death or first hospital admission for heart failure (primary outcome)	CKD vs no CKD 0.63	Y	Y	NO
Cardiovascular death (component outcome)	CKD vs no CKD 0.73	Y	Y	NO

PARADIGM-HF trial (McMurray 2014(14)) with subgroup analysis from Damman 2018(46)				
Outcome	**Interaction p-value** of SUBGROUP CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite of cardiovascular death or first hospital admission for heart failure (primary outcome)	CKD vs no CKD 0.70 4 eGFR categories 0.96	Y	NO (categories)	NO
Cardiovascular death (component outcome)	CKD vs no CKD 0.39 4 eGFR categories 0.75	Y	NO (categories)	NO

First HF hospitalization (component outcome)	CKD vs no CKD 0.83 4 eGFR categories 0.55	Y	NO (categories)	NO
All-cause mortality (Secondary outcome)	CKD vs no CKD 0.27 4 eGFR categories 0.90	Y	NO	NO
Composite renal outcome (first occurrence of any of: 1) a 50% decline in eGFR relative to baseline; 2) >30 ml/min/1.73 m2 decline in eGFR relative to baseline to <60 ml/min/1.73 m2; or 3) reaching end-stage renal disease) **(secondary outcome)**	CKD vs no CKD 0.19 4 eGFR categories 0.37	Y	NO	NO
Decline in eGFR ml/min/1.73 m2/year (exploratory outcome)	CKD vs no CKD 0.54	Y	NO	NO
Post hoc composite renal outcome (either a 50% decrease in the eGFR from baseline or reaching end-stage renal disease)	CKD vs no CKD 0.97	Y	NO	NO
Safety				
serum creatinine ≥ 2.5mg/dl during follow-up	CKD vs no CKD NS	Y	NO	NO
Patients stopping drug for reason other than mortality	CKD vs no CKD 0.18	Y	NO	NO

Patient stopping drug because of renal adverse effect	CKD vs no CKD 0.52	Y	NO	NO

7.3.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

PARADIGM-HF trial (McMurray 2014(14))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite of cardiovascular death or first hospital admission for heart failure (primary outcome)	Overall **HR: 0·80 (0·73–0·87)** **P < 0·001**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: ok
Cardiovascular death	Overall **HR: 0·80 (0·71–0·89)** **P < 0·001**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: ok Imprecision: ok
First HF hospitalization	Overall **HR: 0.79 (0.71 to 0.89)** **P < 0.001**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: ok
All-cause mortality (Secondary outcome)	Overall **HR: 0.84 (0.76 to 0.93)** **P < 0.001**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: ok
Composite renal outcome (first occurrence of any of: 1) a 50% decline in eGFR relative to baseline; 2) >30 ml/min/1.73 m2 decline in eGFR relative to baseline to <60 ml/min/1.73 m2; or 3) reaching end-stage renal disease)	Overall HR: 0.86 (0.65 to 1.13) NS	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: -1 (CI)

(secondary outcome)		
eGFR decline (mL/min per 1·73m² per year) (expl. outcome)	Overall **MD: 0.44 (0.21 to 0.67)** **p < 0.001**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: ok
Post hoc composite renal outcome (either a 50% decrease in the eGFR from baseline or reaching end-stage renal disease)	Overall **HR: 0.63 (0.42–0.95)** **P = 0.028**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: -1 (n events and CI)
serum creatinine ≥ 2.5mg/dl during follow-up	Overall **OR: 0.73 (0.59–0.92)** **P = 0.007**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: ok
Patients stopping drug for reason other than mortality	Overall **HR: (0.80–0.98)** **P = 0.018**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: ok
Patient stopping drug because of renal adverse effect	Overall **HR: 0.49 (0.31–0.76)** **P = 0.0022**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -1 (CKD population 32%) Imprecision: -1 (n events and CI)

7.3.2 Sacubitril/valsartan vs valsartan

7.3.2.1 HFpEF

7.3.2.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that CKD status does not modify the effect of sacubitril/valsartan in comparison to valsartan in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without CKD.

The PARAGON-HF trial (Solomon 2019(15)) compared sacubitril/valsartan with valsartan for the primary composite outcome of time to CV death or total (first and recurrent) hospitalization for heart failure in patients with HFpEF.

The primary composite outcome **did not differ significantly** between **sacubitril/valsartan** and valsartan in the overall population. Because this difference did not meet the predetermined level of statistical significance, **subsequent analyses are to be considered exploratory.**

The consistency of effects in CKD patients versus non-CKD patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect in prespecified analysis** of primary outcome **and in non-prespecified analysis**.

PARAGON-HF trial (Solomon 2019(15))				
Outcome	**Interaction p-value** of SUBGROUP CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite of total hospitalizations for heart failure and death from cardiovascular causes. (primary outcome)	NS	Y	Y	NO

PARAGON-HF trial (Solomon 2019(15))with subgroup analysis from Mc Causland 2020(47)				
Outcome	**Interaction p-value** of SUBGROUP CKD vs no CKD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite renal outcome (defined as either: (1) > 50% decline in eGFR relative to baseline; (2) development of end-stage renal disease; or (3) death attributable to renal causes) **(Primary outcome)**	**0.92**	Y	Y	NO
>50% decline in eGFR	**NS**	Y	NO	NO
End-stage renal disease	**NS**	Y	NO	NO
Safety				
Adverse events requiring study drug discontinuation, serious adverse events, and permanent discontinuation attributable to renal impairment were more common among those with baseline eGFR <60 mL·min–1·1.73 m–2 (versus eGFR > 60 mL·min–1·1.73 m–2).		Y	NO	N.R.

7.3.2.1.2 How much confidence do we have that the overall results are applicable in this specific population?

PARAGON-HF trial (Solomon 2019(15))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite of total hospitalizations for heart failure and death from cardiovascular causes. (primary outcome)	Overall RR: 0.87 (0.75-1.01) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (CKD population 47%) Imprecision: ok
Composite renal outcome (defined as either: (1) > 50% decline in eGFR relative to baseline; (2) development of end-stage renal disease; or (3) death attributable to renal causes) **(Primary outcome)**	Overall **HR: 0.50 (0.33 to 0.77)** **P = 0.001**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 (CKD population 47%) Imprecision: -1 (n events, CI)
>50% decline in eGFR	Overall **HR: 0.44 (0.28 to 0.69)** **SS**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 (CKD population 47%) Imprecision: -1 (n events, CI)
End-stage renal disease	Overall HR: 0.58 (0.23 to 1.47) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 (CKD population 47%) Imprecision: -1 (n events, CI)

8 Heart failure and obesity - Summary and conclusions from the literature review

8.1 SGLT2-inhibitors vs placebo

8.1.1 Dapagliflozin vs placebo

8.1.1.1 HFrEF

8.1.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that BMI does not modify the effect of dapagliflozin in comparison to placebo in patients with heart failure with reduced ejection fraction.

In this case, the overall effect applies to patients in all BMI categories.

The DAPA-HF trial (McMurray 2019(18)) compared dapagliflozin with placebo for the primary composite outcome of worsening heart failure or death from cardiovascular causes in patients with HFrEF.

Dapagliflozin reduced the risk of the primary outcome compared to placebo. Mcmurry 2019 performed a prespecified subgroup analysis for BMI<30 vs BMI≥30 kg/m². However, no interaction test was performed, therefore heterogeneity of efficacy between BMI<30 and BMI ≥30 cannot be evaluated.

Adamson 2021 evaluated the relation between baseline BMI and outcomes in patients enrolled in the DAPA-HF trial. In the analysis plan of the DAPA-HF trial, BMI was categorized into BMI <30 and BMI ≥30 for subgroup analysis. However, Adamson 2021 performed the analysis with a more detailed categorization of BMI (underweight, normal weight, overweight, obesity class I, obesity class II and obesity class III) that was not prespecified in the analysis plan.

In the analysis plan of the DAPA-HF trial, subgroup analyses were planned for the following efficacy outcomes: the primary endpoint, CV death component of the primary composite endpoint and the secondary composite endpoint of CV death or HF hospitalization. Adamson 2021, however, performed subgroup analyses for additional outcomes not mentioned in the analysis plan. The p-values for the subgroup analyses and interaction were not adjusted for multiple comparisons.

<u>Primary outcome and subgroup analysis by BMI category</u>

Dapagliflozin reduced the combined risk of cardiovascular death or worsening heart failure compared to placebo in patients with HFrEF in the DAPA-HF trial. **The interaction test suggests that BMI does not modify the effect of dapagliflozin in comparison to placebo on the primary outcome cardiovascular death or worsening heart failure.**

<u>Secondary outcomes and subgroup analysis by BMI category</u>

Dapagliflozin reduced the risk of total hospitalizations for HF and CV death (recurrent events) compared to placebo in patients with HFrEF in the DAPA-HF trial. **The interaction test suggests that BMI does not modify the effect of dapagliflozin in comparison to placebo for the composite outcome total hospitalizations for HF and CV death (recurrent events).**

Dapagliflozin improved the symptom scores (change in KCCQ total symptom score) after 8 months more than placebo in patients with HFrEF in the DAPA-HF trial. **The interaction test suggests that BMI does not modify the effect of dapagliflozin in comparison to placebo on the outcome "change in KCCQ-TSS at 8 months".**

There was a lower risk for the outcomes CV death, all-cause death, and HF hospitalization/urgent HF visit in the dapagliflozin group compared to the placebo group. **The interaction tests suggest that BMI does not modify the effect of dapagliflozin in comparison to placebo on these 3 outcomes.**

Safety

Adamson 2021 evaluated the relation between baseline BMI and several safety outcomes in patients enrolled in the DAPA-HF trial. None of the interaction tests were statistically significant ($p<0.05$) which suggests that BMI does not modify the risk of the studied adverse events.

DAPA-HF trial (McMurray 2019(18))with subgroup analysis from McMurray 2019(18) ; Adamson 2021(48):				
Outcome	**Interaction p-value** of SUBGROUP BMI>30 vs BMI<30 AND SUBGROUP 4 BMI categories: BMI <25.0 kg/m²; BMI 25.0–29.9 kg/m²; BMI 30.0–34.9 kg/m²; BMI 35.0 -≥40 kg/m²	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
composite outcome of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) **or death from cardiovascular causes (primary outcome)**	BMI>30 vs BMI<30 P interaction not done SUBGROUP 4 BMI 0.79	Y	NO	NO
Total hospitalizations for HF and CV death (recurrent events) Adjusted for history of HF hospitalization (apart from all-cause death) and stratified by diabetes status.	0.63	Y	NO	NO

Change in KCCQ-TSS at 8 months (mean±SD)	0.40	Y	NO	NO
CV death	0.58	Y	NO	NO
All-cause death	0.77	Y	NO	NO
HF Hospitalization/ urgent HF visit	0.67	Y	NO	NO
SAFETY				
• Discontinuation due to adverse event • Volume depletion • Renal adverse event • Bone fracture • Amputation • Major hypoglycaemia	No significant p value for interaction	Y	NO	NO

8.1.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

DAPA-HF trial (McMurray 2019(18))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite outcome of worsening heart failure or death from cardiovascular causes (primary outcome)	**Overall** **386/2373 vs 502/2371** **HR 0.74 (0.65-0.85)** **p<0.001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 35%; BMI>35: 14%) Imprecision: ok
Total hospitalizations for HF and CV death (recurrent events)	**Overall** **567/2373 vs 742/2371** **Rate ratio 0.75 (0.65-0.88)** **p<0.001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 35%; BMI>35: 14%) Imprecision: ok

Change in KCCQ-TSS at 8 months	**Overall** **Difference 6.1±18.6 vs 3.3±19.2** **Difference 1.18 (1.11-1.26)** **p<0.001** **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 35%; BMI>35: 14%) Imprecision: ok
CV death	**Overall** **227/2373 vs 273/2371** **HR 0.82 (0.69-0.98)**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 35%; BMI>35: 14%) Imprecision: ok
All-cause death	**Overall** **276/2373 vs 329/2371** **HR 0.83 (0.71-0.97**)	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 35%; BMI>35: 14%) Imprecision: ok
HF Hospitalization/ urgent HF visit	**Overall** **237/2373 vs 326/2371** **HR 0.70 (0.59-0.83)**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 35%; BMI>35: 14%) Imprecision: ok

8.1.1.2 HFpEF

8.1.1.2.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that BMI does not modify the effect of dapagliflozin in comparison to placebo in patients with heart failure with preserved ejection fraction.

In this case, the overall effect applies to patients in all BMI categories.

The DELIVER trial (Solomon 2022(21)) compared dapagliflozin with placebo for the primary composite outcome of worsening heart failure or death from cardiovascular causes in patients with mildly Reduced or Preserved Ejection Fraction.

Dapagliflozin reduced the risk of the primary outcome compared to placebo. Solomon 2022 performed a prespecified subgroup analysis for BMI<30 vs BMI≥30 kg/m². However, no interaction test was performed, therefore heterogeneity of efficacy between BMI<30 and BMI ≥30 cannot be evaluated.

Adamson 2022 evaluated the relation between baseline BMI and outcomes in patients enrolled in the DELIVER trial. In the analysis plan of the DELIVER trial, BMI was categorized into BMI <30 and BMI for subgroup analysis. However, Adamson 2022 performed the analysis with a more detailed categorization of BMI "to provide more granularity" about the effect of dapagliflozin according to BMI.

In the analysis plan of the DELIVER trial, subgroup analyses were planned for the following efficacy outcomes: the primary endpoint, CV death and the HF event (hospitalization for HF and urgent HF visit) component of the primary composite endpoint. Adamson 2022, however, performed subgroup analyses for additional outcomes not mentioned in the analysis plan. The p-values for the subgroup analyses and interaction were not adjusted for multiple comparisons.

Primary outcome and subgroup analysis by BMI category

Dapagliflozin reduced the combined risk of cardiovascular death or worsening heart failure compared to placebo in patients with HFpEF in the DELIVER trial. **The interaction test suggests that BMI does not modify the effect of dapagliflozin in comparison to placebo on the primary outcome cardiovascular death or worsening heart failure.**

Secondary outcomes and subgroup analysis by BMI category

Dapagliflozin reduced the combined risk of worsening heart failure events (hospitalization for heart failure or an urgent visit) or cardiovascular death compared to placebo in patients with HFpEF in the DELIVER trial. **The interaction test suggests that BMI does not modify the effect of dapagliflozin in comparison to placebo on the composite outcome worsening heart failure events or cardiovascular death.**

Dapagliflozin decreased the symptom burden (change in KCCQ total symptom score) after 8 months more than placebo in patients with HFpEF in the DELIVER trial. **The interaction test suggests that BMI modifies the effect of dapagliflozin in comparison to placebo on the outcome "change in KCCQ-TSS at 8 months".** The improvement in KCCQ-TSS was greatest in patients with the highest BMI. However, this subgroup analysis was not prespecified. **As prespecification of a subgroup analysis is a critical attribute to be considered plausible, further research is necessary before considering taking clinical action on the basis of this result.**
There was a lower risk for the outcome worsening heart failure and no difference in risk for the outcomes CV death and all-cause death in the dapagliflozin group compared to the placebo group. **The interaction tests suggest that BMI does not modify the effect of dapagliflozin in comparison to placebo on these 3 outcomes.**

Safety

Adamson 2022 evaluated the relation between baseline BMI and several safety outcomes in patients enrolled in the DELIVER trial. None of the interaction tests were statistically significant ($p<0.05$) which suggests that BMI does not modify the risk of the studied adverse events.

DELIVER trial (Solomon 2022(21)) subgroup analysis from M Solomon 2022(21); Adamson 2022(49):				
Outcome	**Interaction p-value** of SUBGROUP BMI>30 vs BMI<30 AND SUBGROUP 5 BMI categories: BMI 18.5–24.9 kg/m² ; BMI 25.0–29.9 kg/m²; BMI 30.0–34.9 kg/m²; BMI 35.0–39.9 kg/m²; BMI ≥40 kg/m²	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
composite outcome of worsening heart failure (hospitalization or an urgent visit) **or death from cardiovascular causes (primary outcome)**	BMI>30 vs BMI<30 P interaction not done SUBGROUP 5 BMI 0.82	Y	NO	NO
Worsening heart failure (hospitalization for heart failure or an urgent visit) events and cardiovascular deaths	0.44	Y	NO	NO
Change in KCCQ-TSS at 8 months Placebo-corrected change at 8 months (Mixed-effect models for repeated measurements adjusted for baseline value, visit (Months 1, 4, and 8), randomized treatment, and interaction of treatment and visit.)	0.03	Y	NO	Y
Worsening heart failure event	0.66	Y	NO	NO
Cardiovascular death	0.89	Y	NO	NO

All-cause death	0.82	Y	NO	NO
SAFETY				
• AE leading to discontinuation of randomized treatment • Amputation • Definite or probable DKA • Major hypoglycaemic event • Volume depletion SAE/DAE • Renal SAE/DAE	No significant p value for interaction	Y	NO	NO

8.1.1.2.2 How much confidence do we have that the overall results are applicable in this specific population?

DELIVER trial (Solomon 2022(21))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
composite outcome of worsening heart failure (hospitalization or an urgent visit) **or death from cardiovascular causes (primary outcome)**	**Overall** **512/3131 vs 610/3132** **HR 0.82 (0.73-0.92)** **p<0.001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 45%; BMI>35: 20%) Imprecision: ok
Worsening heart failure (hospitalization for heart failure or an urgent visit) events and cardiovascular deaths	**Overall** **815/3131 vs 1057/3132** **Rate ratio 0.77 (0.67-0.89)** **p<0.001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 45%; BMI>35: 20%) Imprecision: ok
Change in KCCQ-TSS at 8 months Placebo-corrected change at 8 months (Mixed-effect models for repeated measurements adjusted for baseline value,	**Difference 2.4 points (1.5-3.4)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 45%; BMI>35: 20%) Imprecision: ok

visit (Months 1, 4, and 8), randomized treatment, and interaction of treatment and visit.)		
Worsening heart failure event	**Overall** **368/3131 vs 455/3132** **HR 0.79 (0.69–0.91)**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 45%; BMI>35: 20%) Imprecision: ok
Cardiovascular death	Overall 231/3131 vs 261/3132 HR 0.88 (0.74–1.05)	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 45%; BMI>35: 20%) Imprecision: ok
All-cause death	Overall 497/3131 vs 526/3132 HR 0.94 (0.83–1.07)	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 45%; BMI>35: 20%) Imprecision: ok

8.1.2 Empagliflozin vs placebo

8.1.2.1 HFrEF

8.1.2.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that BMI does not modify the effect of empagliflozin in comparison to placebo in patients with heart failure with reduced ejection fraction.

In this case, the overall effect applies to patients in all BMI categories.

The EMPEROR-R trial (Packer 2020) (23)) compared empagliflozin with placebo for the primary composite outcome of cardiovascular mortality or HF hospitalization in patients with HFrEF.

Empagliflozin reduced the risk of the primary outcome compared to placebo. Packer 2022 performed a prespecified subgroup analysis for BMI<30 vs BMI≥30 kg/m². However, no interaction test was performed, therefore heterogeneity of efficacy between BMI<30 and BMI ≥30 cannot be evaluated.

Anker 2023 evaluated the relation between baseline BMI and outcomes in patients enrolled in the EMPEROR-R trial. In the analysis plan of the EMPEROR-R trial, BMI was categorized into BMI <30 and

BMI for subgroup analysis. However, Anker 2023 performed the analysis with a more detailed categorization of BMI that was not prespecified in the analysis plan.

In the analysis plan of the EMPEROR-R trial, subgroup analyses were planned for the following efficacy outcomes: the primary endpoint, time to cardiovascular death, time to first HHF, HHF (first and recurrent), and renal slope. Anker 2023, however, performed subgroup analyses for additional outcomes not mentioned in the analysis plan: all-cause mortality, composite renal endpoint, and changes in KCCQ clinical summary score at week 52. The p-values for the subgroup analyses and interaction were not adjusted for multiple comparisons.

Primary outcome and subgroup analysis by BMI category

Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure compared to placebo in patients with HFrEF in the EMPEROR-R trial. **The interaction test suggests that BMI does not modify the effect of empagliflozin in comparison to placebo on the primary outcome cardiovascular death or worsening heart failure.**

Secondary outcomes and subgroup analysis by BMI category

Empagliflozin reduced the risk of hospitalization for heart failure compared to placebo in patients with HFrEF in the EMPEROR-R trial. **The interaction test suggests that BMI does not modify the effect of empagliflozin in comparison to placebo on the outcome total HHF.**

Empagliflozin reduced the rate of the decline in the estimated GFR over the duration of the double-blind treatment period ("renal slope") compared to placebo in patients with HFrEF in the EMPEROR-R trial. **The interaction test suggests that BMI does not modify the effect of empagliflozin in comparison to placebo on the outcome "renal slope".**

In the EMPEROR-R trial, there was a lower risk for the outcome first hospitalization for heart failure (HHF) in the empagliflozin group compared to the placebo group. **The interaction test suggests that BMI modifies the effect of empagliflozin in comparison to placebo on the outcome "first HHF". However, this subgroup analysis was not prespecified. As prespecification of a subgroup analysis is a critical attribute to be considered plausible, further research is necessary before considering taking clinical action on the basis of this result.**
There was a lower risk for a composite renal endpoint and an improved health status at week 52 in the empagliflozin group compared to the placebo group; and no difference in risk for the outcomes CV death and all-cause death. **The interaction tests suggest that BMI does not modify the effect of empagliflozin in comparison to placebo on these 4 outcomes.**

Safety

Anker 2023 described adverse events across BMI categories and treatment arms. No formal statistical tests were performed.

EMPEROR-R trial (Packer 2020) (23)) with subgroup analysis from Anker 2023(50):				
Outcome	**Interaction p-value** of SUBGROUP BMI>30 vs BMI<30 AND SUBGROUP 5 BMI categories: BMI <20 kg/m2 BMI 20 to <25 kg/m2 BMI 25 to <30 kg/m2 BMI 30 to <35 kg/m2 BMI ≥35 kg/m2	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	BMI>30 vs BMI<30 P interaction not done SUBGROUP 5 BMI 0.32	Y	NO	NO
Total HHF	0.31	Y	NO	NO
Renal slope (eGFR mean slope change/year)	0.67	Y	NO	NO
First HHF	0.04	Y	NO	Y
CV death	0.86	Y	NO	NO
All-cause mortality	0.99	Y	NO	Y
Composite renal endpoint (the need for chronic dialysis or renal transplant or a ≥40% sustained reduction in eGFR or a sustained eGFR <15ml/min/1.73 m2 (if baseline eGFR was ≥30 ml/min/1.73 m2) or <10 ml/min/1.73 m2 (if baseline eGFR was <30 ml/min/1.73 m2)	0.76	Y	NO	Y

Changes in KCCQ clinical summary score at week 52	0.99	Y	NO	Y

8.1.2.1.2 How much confidence do we have that the overall results are applicable in this specific population?

EMPEROR-R trial (Packer 2020(23))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall 361/1863 vs 462/1867 HR 0.75 (0.65-0.86) p<0.001 **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 40%; BMI>35: 11%) Imprecision: ok
Total HHF	Overall HR 0.70 (0.58, 0.85) p<0.001 **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 40%; BMI>35: 11%) Imprecision: ok
Renal slope (eGFR mean slope change/year)	Overall Difference 1.73 (1.10, 2.37) p<0.001 **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 40%; BMI>35: 11%) Imprecision: ok
First HHF	**Overall** **246/1863 vs 342/1867** **HR 0.69 (0.59, 0.81)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 40%; BMI>35: 11%) Imprecision: ok
CV death	Overall HR 0.92 (0.75, 1.12)	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 40%; BMI>35: 11%) Imprecision: -1
All-cause mortality	Overall HR 0.92 (0.77, 1.10)	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 40%; BMI>35: 11%) Imprecision: -1
Composite renal endpoint (the need for chronic dialysis or renal transplant or	**Overall** **HR 0.50 (0.32-0.77)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok

a ≥40% sustained reduction in eGFR or a sustained eGFR <15ml/min/1.73 m2 (if baseline eGFR was ≥30 ml/min/1.73 m2) or <10 ml/min/1.73 m2 (if baseline eGFR was <30 ml/min/1.73 m2)		Consistency: NA Directness: -1 (BMI>30 population 40%; BMI>35: 11%) Imprecision: ok
Changes in KCCQ clinical summary score at week 52	**Overall** **Difference 1.61 (0.39, 2.84)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 40%; BMI>35: 11%) Imprecision: ok

8.1.2.2 HFpEF

8.1.2.2.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that BMI does not modify the effect of empagliflozin in comparison to placebo in patients with heart failure with preserved ejection fraction.

In this case, the overall effect applies to patients in all BMI categories.

Anker 2021a(26) is the main publication of the EMPEROR-P trial that compared empagliflozin with placebo for the primary composite outcome of cardiovascular mortality or HF hospitalization in patients with HFpEF.

Empagliflozin reduced the risk of the primary outcome compared to placebo. Anker 2021 performed a prespecified subgroup analysis for BMI<30 vs BMI≥30 kg/m. However, no interaction test was performed, therefore heterogeneity of efficacy between BMI<30 and BMI ≥30 cannot be evaluated.

Siddiqi 2023(28) evaluated health status across major subgroups of patients enrolled in the EMPEROR-P trial. Health status was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ). Change in KCCQ clinical summary score at 52 weeks was a key secondary endpoint in the EMPEROR-P trial.

In the analysis plan of the EMPEROR-P trial, BMI was categorized into BMI <30 and BMI for subgroup analysis. However, Siddiqi 2023 performed the analysis with a more detailed categorization of BMI that was not prespecified in the analysis plan. Subgroup analysis for the outcome “changes in KCCQ” was not prespecified in the analysis plan. No adjustments were made for multiple comparisons.

In the EMPEROR-P trial, there was a higher improvement in health status at week 52 in the empagliflozin-group compared to placebo-group in patients with HFpEF. **The interaction test suggests that BMI does not modify the effect of empagliflozin in comparison to placebo on the outcome “KCCQ CSS at week 52”.**

Siddiqi 2023 repeated their analysis for other components of the KCCQ at week 52: changes of KCCQ total symptom score and KCCQ overall summary score. The p-values of the interaction test were respectively 0.080 and 0.078. These outcomes were not secondary outcomes in the EMPEROR-P trial and these subgroup analyses were also not prespecified in the analysis plan. Results for all patients (regardless of BMI-category) were not reported by the authors.

EMPEROR-P trial (Anker 2021a(26))with subgroup analysis from Siddiqi 2023(28):				
Outcome	**Interaction p-value** of SUBGROUP BMI>30 vs BMI<30 AND SUBGROUP 4 BMI categories: BMI < 25 kg/m² BMI 25 - <30 kg/m² BMI 30 - <35 kg/m² BMI ≥35 kg/m²	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite outcome cardiovascular mortality or HF hospitalization	**Interaction test**: not done	Y	Y	N
Change in KCCQ clinical summary score at week 52	**Interaction test**: p=0.153	Y	N	N

8.1.2.2.2 How much confidence do we have that the overall results are applicable in this specific population?

EMPEROR-P trial (Anker 2021a(26))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite outcome cardiovascular mortality or HF hospitalization	Overall 415/2997 vs 511/2991 HR 0.79 (0.69-0.90) p<0.001 **SS**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 45%) Imprecision: ok
Change in KCCQ clinical summary score at week 52	Overall 4.51±0.31 vs 3.18±0.31 Difference 1.32 (0.45-2.19)	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 45%) Imprecision: ok

8.2 Mineralocorticoid receptor antagonists versus placebo

8.2.1 Eplerenone vs placebo

8.2.1.1 HFrEF

8.2.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that BMI does not modify the effect of eplerenone in comparison to placebo in patients with heart failure with reduced ejection fraction.

In this case, the overall effect applies to patients in all BMI categories.

The EMPHASIS-HF trial (Zannad 2011(29)) compared eplerenone with placebo for the primary composite outcome of cardiovascular mortality or a first HF hospitalization in patients with HFrEF.

Olivier 2017(51) evaluated the interaction between increased adiposity estimated by the waist circumference (WC) and BMI, and the clinical benefit from the eplerenone in patients enrolled in the EMPAHSIS-HF trial. Subgroup analyses according to WC or BMI were not prespecified in the protocol of the trial.

Primary outcome and subgroup analysis by BMI and WC

Eplerenone reduced the combined risk of cardiovascular death or hospitalization for heart failure (HHF) compared to placebo in patients with HFrEF in the EMPHASIS-HF trial. **The interaction test suggests that WC modifies the effect of eplerenone in comparison to placebo on the primary outcome cardiovascular death or HHF.** The effect might be more pronounced in patients with a high WC (≥102 cm and ≥88 cm for men and women, respectively). **However, the subgroup analysis was not prespecified. As prespecification of a subgroup analysis is a critical attribute to be considered plausible, further research is necessary before considering taking clinical action on the basis of this result.**

The interaction test according to BMI was not statistically significant.

Secondary outcomes and subgroup analysis by BMI and WC

In the EMPHASIS-HF trial, there was a lower risk for all-cause mortality, cardiovascular death, and hospitalization for HF in the eplerenone-group compared to the placebo-group. **The interaction tests suggest that BMI or WC do not modify the effect of eplerenone in comparison to placebo on these 3 outcomes.**

Safety

Olivier 2017 evaluated the relation between baseline BMI and WC and several safety outcomes in patients enrolled in the EMPHASIS-HF trial. Detailed results with interaction p-values can be found in the appendix. **The interaction test suggests that WC modifies the effect of eplerenone in comparison to placebo on the outcome "adverse events leading to study-druq withdrawal".** Adverse events leading to eplerenone withdrawal occurred more in patients with a normal WC than in patients with a high WC. **However, the subgroup analysis was not prespecified. As prespecification of a subgroup analysis is a critical attribute to be considered plausible, further research is necessary before considering taking clinical action on the basis of this result.**

EMPHASIS-HF trial (Zannad 2011(29)) with subgroup analysis from Olivier 2017(51)				
Outcome	**Interaction p-value** of SUBGROUP BMI>30 vs BMI<30 AND SUBGROUP NWC (normal waist circumference) vs HWC (high waist circumference) [2]	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	BMI>30 vs BMI<30 P 0.11	Y	NO	NO
	SUBGROUP NWC vs HWC P 0.01	Y	NO	Y
All-cause mortality	BMI>30 vs BMI<30 P 0.73 SUBGROUP NWC vs HWC 0.13	Y	NO	NO
Cardiovascular death	BMI>30 vs BMI<30 P 0.93 SUBGROUP NWC vs HWC 0.09	Y	NO	NO

Hospitalization for HF	BMI>30 vs BMI<30 P 0.25 SUBGROUP NWC vs HWC 0.07	Y	NO	NO
SAFETY				
Adverse events leading to study-drug withdrawal	BMI>30 vs BMI<30 P 0.81	Y	NO	NO
	SUBGROUP NWC vs HWC 0.01	Y	NO	Y

8.2.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

EMPHASIS-HF trial (Zannad 2011(29))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall 229/1287 vs 335/1292 HR 0.63 (0.52-0.75) p<0.0001 **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 27%; HWC: 50%) Imprecision: ok
All-cause mortality	Overall 160/1287 vs 201/1292 HR 0.76 (0.61-0.95) p= 0.01 **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 27%; HWC: 50%) Imprecision: ok
Cardiovascular death	Overall 136/1287 vs 175/1292 HR 0.73 (0.58-0.93) p= 0.009 **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (BMI>30 population 27%; HWC: 50%) Imprecision: ok
Hospitalization for HF	Overall 151/1287 vs 238/1292 HR 0.59 (0.48-0.73) p<0.0001	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: NA

	SS	Directness: -1 (BMI>30 population 27%; HWC: 50%) Imprecision: ok

8.2.2 Spironolactone vs placebo

8.2.2.1 HFpEF

8.2.2.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that BMI does not modify the effect of spironolactone in comparison to placebo in patients with heart failure with preserved ejection fraction.

In this case, the overall effect applies to patients in all BMI categories.

The TOPCAT trial (Pitt 2014(33)) compared spironolactone with placebo for the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure in patients with HFpEF. Overall, the group assigned to spironolactone did not achieve a significant reduction in the primary outcome. Post hoc analyses ("TOPCAT Americas"; Pfeffer 2014(44)) identified important regional differences (patient characteristics, outcomes etc.) between patients randomized from the Americas cohort and from Russia/Georgia.

Elkholey 2021(13) studied the effect of obesity, defined by BMI and waist circumference (WC), on response to spironolactone in the Americas cohort from the TOPCAT trial. It concerns a subgroup analysis of a post hoc analysis in a subpopulation of the TOPCAT trial. Detailed results per BMI- or WC category can be found in the appendix.

Primary outcome and subgroup analysis by BMI and WC

There was no difference in the primary composite outcome cardiovascular death, aborted cardiac arrest or hospitalization for heart failure (HHF) between spironolactone and placebo in patients with HFpEF in the TOPCAT trial (Americas cohort). **The interaction tests suggest that BMI or WC do not modify the effect of spironolactone in comparison to placebo on the primary composite outcome cardiovascular death, aborted cardiac arrest or HHF.**

Secondary outcomes and subgroup analysis by BMI and WC

There was no difference in outcome cardiovascular death, all-cause death, and HHF between spironolactone and placebo in patients with HFpEF in the TOPCAT trial (Americas cohort). **The interaction tests suggest that BMI or WC do not modify the effect of spironolactone in comparison to placebo on these 3 outcomes.**

TOPCAT Americas (Pfeffer 2014(44)), with subgroup analysis from Elkholey 2021(13)				
Outcome	**Interaction p-value** of SUBGROUP BMI>30 vs BMI<30 AND SUBGROUP NWC (normal waist circumference) vs HWC (high waist circumference) [2]	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite of cardiovascular death, HF hospitalization, or aborted cardiac arrest (primary outcome)	BMI>30 vs BMI<30 0.056 SUBGROUP NWC vs HWC 0.930	Y	N	N
Cardiovascular death	BMI>30 vs BMI<30 0.412 SUBGROUP NWC vs HWC 0.887	Y	N	N
All-cause death	BMI>30 vs BMI<30 0.734 SUBGROUP NWC vs HWC 0.757	Y	N	N
HF hospitalizations	BMI>30 vs BMI<30 0.130 SUBGROUP NWC vs HWC 0.990	Y	N	N

8.2.2.1.2 How much confidence do we have that the overall results are applicable in this specific population?

TOPCAT Americas (Pfeffer 2014(44))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite of cardiovascular death, HF hospitalization, or aborted cardiac arrest (primary outcome)	Overall in TOPCAT Americas cohort BMI-analysis HR 1.003 (0.98-1.44); p= 0.987	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (subgroup analysis) Consistency: NA Directness: -1 (BMI>30 population 66%; HWC 79%) Imprecision: -1

	WC analysis HR 1.03 (0.73-1.47); p= 0.834	
Cardiovascular death	Overall in TOPCAT Americas cohort BMI-analysis HR 0.81 (0.58-1.02); p= 0.417 WC analysis HR 0.84 (0.50-1.40); p= 0.513	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (subgroup analysis) Consistency: NA Directness: -1 (BMI>30 population 66%; HWC 79%) Imprecision: -1
All-cause death	Overall in TOPCAT Americas cohort BMI-analysis HR 0.85 (0.69-1.06); p= 0.411 WC analysis HR 1.05 (0.72-1.55); p= 0.76	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (subgroup analysis) Consistency: NA Directness: -1 (BMI>30 population 66%; HWC 79%) Imprecision: -1
HF hospitalizations	Overall in TOPCAT Americas cohort BMI-analysis HR 1.11 (0.77-1.62); p= 0.574 WC analysis HR 1.30 (0.84-2.02; p= 0.221	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (subgroup analysis) Consistency: NA Directness: -1 (BMI>30 population 66%; HWC 79%) Imprecision: -1

9 Heart failure and COPD - Summary and conclusions from the literature review

9.1 SGLT-2 inhibitors

9.1.1 Dapagliflozin vs placebo

9.1.1.1 HFrEF

9.1.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that COPD status (history of COPD yes/no, with no indication of severity) does not modify the effect of dapagliflozin in comparison to placebo in patients with heart failure with reduced ejection fraction.
In this case, the overall effect applies to patients with and without COPD.

The DAPA-HF trial (McMurray 2019(18))compared dapagliflozin with placebo for the primary composite outcome of cardiovascular mortality or worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) in patients with HFrEF.
Dapagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in COPD patients versus non-COPD patients was evaluated in non-prespecified subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in any outcomes.
COPD status was based on investigator-reported medical history; it was not formally diagnosed or evaluated at baseline in this study; and no indication of severity was recorded.

DAPA-HF trial (McMurray 2019(18))with subgroup analysis from Dewan 2021(16)				
Outcome	**Interaction p-value** of SUBGROUP COPD vs no COPD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome of main trial; analysis not prespecified for this subgroup)**	0.47	Y	NO	NO
Worsening HF event	0.42	Y	NO	NO
First HF hospitalization	0.35	Y	NO	NO
CV Death	0.47	Y	NO	NO

Total HF hospitalization/CV death	0.71	Y	NO	NO
Death from any cause	0.96	Y	NO	NO
Change in KCCQ total symptom score at 8 mo	0.71	Y	NO	NO
SAFETY				
AE related study drug discontinuation	0.59	Y	NO	NO
Volume depletion	0.96	Y	NO	NO
Renal AE	0.81	Y	NO	NO

9.1.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

DAPA-HF trial (McMurray 2019(18))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome of main trial; analysis not prespecified for this subgroup)**	**Overall** **HR 0.74 (0.65 to 0.85)** **P<0.001**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
Worsening HF event	**Overall** **HR 0.70 (0.59 to 0.83)** **P NA**	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness-2 (COPD population 12.3%; no differentiation in severity)

		Imprecision: ok
First HF hospitalization	**Overall** **HR 0.70 (0.59 to 0.83)** **P NA**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
CV Death	**Overall** **HR 0.82 (0.69 to 0.98)** **P NA**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
Total HF hospitalization/CV death	**Overall** **RR 0.75 (0.65 to 0.88)** **P<0.001** **SS**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
Death from any cause	**Overall** **HR 0.83 (0.71 to 0.97)**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
Change in KCCQ total symptom score at 8 mo	**Overall** **RR 1.18 (1.11 to 1.26)**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
AE related study drug discontinuation	Overall Dapagliflozin: 111/2368 (4.7%) Placebo: 116/2368 (4.9%) P 0.79	Unable to assess
Volume depletion	Overall Dapagliflozin: 178/2368 (7.5%) Placebo: 162/2368 (6.8%) P 0.40	Unable to assess
Renal AE	Overall Dapagliflozin: 153/2368 (6.5%) Placebo: 170/2368 (7.2%) P 0.36	Unable to assess

9.1.1.2 HFpEF

9.1.1.2.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that COPD status (history of COPD yes/no, with no indication of severity) does not modify the effect of dapagliflozin in comparison to placebo in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without COPD.

The DELIVER trial (Solomon 2022(21)) compared dapagliflozin with placebo for the primary composite outcome of worsening heart failure, which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure, or cardiovascular death in patients with HFpEF.
Dapagliflozin reduced the risk of the primary outcome compared to placebo in the overall population.
The consistency of effects in COPD patients versus non-COPD patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect** in prespecified and non-prespecified outcomes.
COPD status was based on investigator-reported medical history; it was not formally diagnosed or evaluated at baseline in this study; and no indication of severity was recorded.

DELIVER trial (Solomon 2022(21)) with subgroup analysis from Butt 2023(52)				
Outcome	**Interaction p-value** of COPD vs no COPD subgroups	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite of worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	0.98	Y	NO	NO
Composite of cardiovascular death and all heart failure events (including recurrent)	0.70	Y	NO	NO
Heart failure hospitalization	0.90	Y	NO	NO
Cardiovascular hospitalizations	0.69	Y	NO	NO
All-cause hospitalizations	0.96	Y	NO	NO
CV death	0.35	Y	NO	NO
Death from any cause	0.59	Y	NO	NO

All-cause deaths and all-cause hospitalizations	0.83	Y	NO	NO
KCCQ-TSS (change from baseline to 8 months)	0.78	Y	NO	NO
SAFETY				
• Discontinuation of study drug due to adverse event • Volume depletion • Renal adverse event • Amputation • Major hypoglycemia Diabetic ketoacidosis	No significant p-value for interaction	Y	NO	NO

9.1.1.2.2 How much confidence do we have that the overall results are applicable in this specific population?

DELIVER trial (Solomon 2022(21))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite of worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	**Overall** **HR 0.82 (0.73-0.92)** **p<0.001** **SS**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
Composite of cardiovascular death and all heart failure events (including recurrent)	**Overall** **RR 0.77 (0.67 to 0.89)** **P <0.001** **SS**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
Heart failure hospitalization	**Overall** **RR 0.77 (0.67-0.89)** **P NA**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok

Cardiovascular hospitalizations	Overall group Not reported	Unable to assess
All-cause hospitalizations	Overall group Not reported	Unable to assess
CV death	Overall HR 0.88 (0.74 to 1.05) P NA	⨁⨁⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
Death from any cause	Overall HR 0.94 (0.83 to 1.07) P NA	⨁⨁⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
All-cause deaths and all-cause hospitalizations	Overall group Not reported	Unable to assess
KCCQ-TSS (change from baseline to 8 months)	**Overall** **1.11 (1.03–1.21)** **P 0.009**	⨁⨁⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.3%; no differentiation in severity) Imprecision: ok
SAFETY		
• **Discontinuation of study drug due to adverse event** • **Volume depletion** • **Renal adverse event** • **Amputation** • **Major hypoglycemia** • **Diabetic ketoacidosis**	No statistical analysis reported for overall group	Unable to assess

9.2 ARNI

9.2.1 Sacubitril/valsartan vs enalapril

9.2.1.1 HFrEF

9.2.1.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that COPD status does not modify the effect of sacubitril/valsartan in comparison to enalapril in patients with heart failure with reduced ejection fraction.
In this case, the overall effect applies to patients with and without COPD.

The PARADIGM-HF trial (McMurray 2014(14)) compared sacubitril/valsartan with enalapril for the primary composite outcome of time to CV death or first hospitalization for heart failure in patients with HFrEF. **Of note: this trial excluded patients with severe pulmonary disease (including severe COPD).**
Sacubitril/valsartan reduced the risk of the primary outcome compared to enalapril in the overall population.
The consistency of effects in COPD patients versus non-COPD patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect in non-prespecified analysis**.

PARADIGM-HF trial (McMurray 2014(14)) with subgroup analysis from Ehteshami-Afshar 2021(53)				
Outcome	**Interaction p-value** of SUBGROUP COPD vs no COPD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite of cardiovascular death or total hospital admission for heart failure (Primary outcome)	0.17	Y	NO	NO
Cardiovascular death (component outcome)	0.24	Y	NO	NO
First HF hospitalization (component outcome)	0.43	Y	NO	NO
All-cause mortality (Secondary outcome)	0.64	Y	NO	NO
KCCQ CSS at 8 months (Secondary outcome)	0.45	Y	NO	NO
CV hospitalization (post hoc outcome)	0.055	Y	NO	NO

9.2.1.1.2 How much confidence do we have that the overall results are applicable in this specific population?

PARADIGM-HF trial (McMurray 2014(14))

Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite of cardiovascular death or first hospital admission for heart failure (primary outcome)	Overall **HR : 0·80 (0·73–0·87)** **P < 0·001**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.9%) Imprecision: ok
Cardiovascular death (component outcome)	Overall **HR : 0·80 (0·71–0·89)** **P < 0·001**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.9%) Imprecision: ok
First HF hospitalization (component outcome)	Overall **HR: 0.79 (0.71 to 0.89)** **P <0.001**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.9%) Imprecision: ok
All-cause mortality (Secondary outcome)	Overall **HR: 0.84 (0.76 to 0.93)** **P <0.001**	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.9%) Imprecision: ok
Mean change in KCCQ at 8 mo (SE) (secondary outcome)	Overall MD: 1.64 (0.63–2.65) p = 0.001	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 12.9%) Imprecision: ok
CV hospitalization	Overall Not reported	Insufficient data

9.2.2 Sacubitril/valsartan vs valsartan

9.2.2.1 HFpEF

9.2.2.1.1 Are the results of the subgroup analysis and the overall analysis different?

Subgroup analyses suggest that COPD status does not modify the effect of sacubitril/valsartan in comparison to valsartan in patients with heart failure with preserved ejection fraction.
In this case, the overall effect applies to patients with and without COPD.

The PARAGON-HF trial (Solomon 2019(15)) compared sacubitril/valsartan with valsartan for the primary composite outcome of time to CV death or total (first and recurrent) hospitalization for heart failure in patients with HFpEF. **Of note: this trial excluded patients with severe pulmonary disease (including severe COPD).**

The primary composite outcome **did not differ significantly** between **sacubitril/valsartan** and valsartan in the overall population. Because this difference did not meet the predetermined level of statistical significance, **subsequent analyses are to be considered exploratory.**

The consistency of effects in COPD patients versus non-COPD patients was evaluated in subgroup analyses. The test for subgroup differences indicates that there is **no statistically significant subgroup effect in non-prespecified analysis**.

PARAGON-HF trial (Solomon 2019(15)) with subgroup analysis from Mooney 2021 (54)				
Outcome	**Interaction p-value** of SUBGROUP COPD vs no COPD	Evaluation of SUBGROUP		
		Baseline characteristic	Prespecified	Test of interaction p<0.05
Composite of cardiovascular death or total hospital admission for heart failure (Primary outcome)	0.66	Y	NO	NO
Cardiovascular death (component outcome)	0.43	Y	NO	NO
Total HF hospitalization (component outcome)	0.50	Y	NO	NO
All-cause mortality (Secondary outcome)	0.39	Y	NO	NO
KCCQ CSS at 8 months (Secondary outcome)	0.51	Y	NO	NO

9.2.2.1.2 How much confidence do we have that the overall results are applicable in this specific population?

PARAGON-HF trial (Solomon 2019(15))		
Outcome	**Result (95%CI)**	**Quality of the evidence (GRADE)**
Composite of total hospitalizations for heart failure and death from cardiovascular causes.	Overall RR: 0.87 (0.75-1.01) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 14%) Imprecision: ok

(primary outcome)		
CV death (component outcome)	Overall HR: 0.95 (0.79–1.16) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 14%) Imprecision: ok
Total HF hospitalization (component outcome)	Overall RR: 0.85 (0.72–1.00) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 14%) Imprecision: ok
All-cause mortality (Secondary outcome)	Overall HR: 0.97 (0.84-1.13) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 14%) Imprecision: ok
KCCQ CSS at 8 months (Secondary outcome)	Overall MD: 1.0 (0.0–2.1) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: ok Consistency: NA Directness: -2 (COPD population 14%) Imprecision: -1 (CI)

10 Heart failure and other comorbidities- Summary and conclusions from the literature review

Our search did not yield results corresponding to our inclusion criteria for the following comorbidities:

- Pulmonary hypertension
- Cachexia
- Sarcopenia

11 Additional safety information from other sources

11.1 Drugs used in heart failure

11.1.1 Diuretics: thiazides and related products

L'hydrochlorothiazide est le seul thiazide commercialisé en Belgique, et est uniquement disponible sous forme d'association. La chlorthalidone et l'indapamide sont en revanche disponibles en monopréparation.(7) / Hydrochloorthiazide is het enige thiazide beschikbaar op de Belgische markt en dit enkel in combinatiepreparaten ; chloortalidon en indapamide zijn wel als monopreparaat beschikbaar. (7)

11.1.1.1 Contraindications (among the selected comorbidities of HF)

- Insuffisance rénale sévère (RCP) (7) / Ernstige nierinsufficiëntie (SKP) (7)
- Most thiazides are not effective in patients with a creatinine clearance of less than 30 mL/minute. They should not be used in patients with severe renal impairment or anuria.(8)

11.1.1.2 Interactions (with drugs used in the selected comorbidities of HF)

- Hypokalaemia intensifies the effect of digitalis on cardiac muscle. (8)
- Risque accru de toxicité des digitaliques en cas d'hypokaliémie. (7)/
  Verhoogd risico op toxiciteit van digitalis bij hypokaliëmie.(7)
- The potassium-depleting effect of diuretics may be enhanced e.a. by corticosteroids or beta2 agonists such as salbutamol(8)
- Chlortalidone has been associated with a reduction in warfarin's activity in healthy subjects and it has been suggested that this might be a consequence of the diuresis concentrating the circulating clotting factors. (8)

11.1.1.3 Additional precautions and monitoring in cases of comorbidity

- Les thiazides et apparentés sont moins efficaces en cas d'insuffisance rénale sévère (clairance de la créatinine < 30 ml/min). (7) / Thiaziden en aanverwanten zijn minder doeltreffend bij ernstige nierinsufficiëntie (creatinineklaring < 30 ml/min). (7)
- Hydrochlorothiazide and other thiazide diuretics may cause metabolic disturbances especially at high doses. They may provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. They may aggravate or unmask diabetes mellitus. (8)
- Augmentation de la résistance à l'insuline avec augmentation de la glycémie et hypertriglycéridémie, surtout à fortes doses. Il n'est pas clair quelle en est la pertinence clinique à long terme, étant donné que, malgré ces effets, les thiazides entraînent une diminution de la mortalité et de la morbidité cardio-vasculaires, même chez les patients diabétiques. (7) / Toename van de insulineresistentie met verhogen van de glykemie en hypertriglyceridemie, vooral bij hoge doses. De klinische relevantie hiervan op lange termijn is onduidelijk aangezien, ondanks deze effecten, met thiaziden toch een daling van de cardiovasculaire mortaliteit en morbiditeit bekomen wordt, ook bij diabetici. (7)
- Blood-glucose concentrations should be monitored in patients taking antidiabetics, since requirements may change. (8)
- Diuretics should also be given with caution in renal impairment since they can further reduce renal function. (8)

11.1.2 Loop diuretics

- Contrairement aux thiazides, les diurétiques de l'anse à doses élevées conservent leur action diurétique même en cas de diminution sévère de la fonction rénale. (7) /De lisdiuretica onderscheiden zich van de thiaziden door een hoger maximaal natriuretisch effect en een grotere klaring van vrij water. (7)
- Precautions for furosemide that are dependent on its effects on fluid and electrolyte balance are similar to those of the thiazide diuretics (8)

11.1.2.1 Interactions (with drugs used in the comorbidities selected in HF))

The interactions of furosemide that are due to its effects on fluid, electrolyte, and carbohydrate balance are similar to those of hydrochlorothiazide. The risk of hypokalaemia may be less with loop diuretics such as furosemide, which have a short duration of action, than with thiazide diuretics.

- Hypokalaemia intensifies the effect of digitalis on cardiac muscle. (8)
  Risque accru de toxicité des digitaliques en cas d'hypokaliémie. (7) / Verhoogd risico op toxiciteit van digitalis bij hypokaliëmie.(7)
- The potassium-depleting effect of diuretics may be enhanced e.a. by corticosteroids or beta2 agonists such as salbutamol. (8)
- Torasemide has been reported to enhance the activity of warfarin, possibly by competing for metabolism through the cytochrome P450 isoenzyme CYP2C9 and by displacement of warfarin from protein-binding sites. However, bumetanide, furosemide, and the thiazides appear to have no effect on warfarin. (8)

11.1.2.2 Additional precautions and monitoring in cases of comorbidity

- Precautions for furosemide that are dependent on its effects on fluid and electrolyte balance are similar to those of the thiazide diuretics Hydrochlorothiazide and other thiazide diuretics may cause metabolic disturbances especially at high doses.[…] They may provoke hyperglycaemia and glycosuria in diabetic and other susceptible patients. They may aggravate or unmask diabetes mellitus. (8)
- Augmentation de la résistance à l'insuline avec augmentation de la glycémie et hypertriglycéridémie, surtout à fortes doses Il n'est pas clair quelle en est la pertinence clinique à long terme, la pertinence clinique à long terme n'est pas claire. (7) /
  Toename van de insulineresistentie met verhogen van de glykemie en hypertriglyceridemie, vooral bij hoge doses. De klinische relevantie hiervan op lange termijn is onduidelijk. (7)
- Blood-glucose concentrations should be monitored in patients taking antidiabetics, since requirements may change. (8)
- Although furosemide is used in high doses for oliguria due to chronic or acute renal impairment it should not be given in anuria or in renal failure caused by nephrotoxic or hepatotoxic drugs nor in renal failure associated with hepatic coma. (8)

11.1.3 Mineralocorticoid receptor antagonists

Remarque : Selon le RCP la finérénone a pour indication l'insuffisance rénale chronique (avec albuminurie) associée au diabète de type 2. L'insuffisance cardiaque n'est pas reprise dans ses indications. (7) / *Opmerking: Volgens de SKP is finerenon geïndiceerd voor chronisch nierfalen (met albuminurie) geassocieerd met type 2 diabetes. Hartfalen valt niet onder de indicaties.* (7)

11.1.3.1 Contraindications (among the selected comorbidities of HF)

- Eplérénone et spironolactone: insuffisance rénale sévère (RCP). (7) /
  Eplerenon en spironolacton: ernstige nierinsufficiëntie (SKP). (7)

11.1.3.2 Interactions (with drugs used in the comorbidities selected in HF)

- Spironolactone has been associated with a reduction in warfarin's activity in healthy subjects and it has been suggested that this might be a consequence of the diuresis concentrating the circulating clotting factors. (8)

11.1.3.3 Special precautions and monitoring in cases of comorbidity

- En cas d'insuffisance rénale modérée à sévère: risque accru d'hyperkaliémie. (7) /
  Matige tot ernstige nierinsufficiëntie: verhoogd risico van hyperkaliëmie. (7)

- Risque accru d'hyperkaliémie en cas d'association à d'autres médicaments épargneurs de potassium (notamment des diurétiques d'épargne potassique, des sartans); ce risque est surtout élevé en cas d'insuffisance rénale.
  Même avec les faibles doses de spironolactone et d'éplérénone utilisées dans le traitement de l'insuffisance cardiaque, une hyperkaliémie peut survenir, vu que des IECA ou des sartans sont souvent utilisés concomitamment. (7)
  / Stijging van de kaliëmie bij associëren met kaliumsupplementen of met andere kaliumsparende middelen (o.a. ACE-inhibitoren en sartanen); dit risico is bijzonder hoog bij nierinsufficiëntie.
  Ook met de lage doses spironolacton en eplerenon gebruikt bij de behandeling van hartfalen kan hyperkaliëmie optreden, omdat daarbij dikwijls ook ACE-inhibitoren of sartanen worden gebruikt. (7)

- Spironolactone should be used with care in patients who are at increased risk of developing hyperkalaemia; such patients include those with diabetes mellitus, and those with some degree of renal impairment. (8)

- Finérénone : **L'hyperkaliémie** reste une préoccupation majeure lors de l'utilisation d'antagonistes des récepteurs des minéralocorticoïdes, en particulier chez les patients en insuffisance rénale. Bien que les chercheurs affirment que la finérénone provoquerait moins fréquemment une hyperkaliémie que la spironolactone ou l'éplérénone, ceci est peu documenté dans le cadre d'études cliniques. Le risque d'hyperkaliémie peut être encore accru par les interactions éventuelles avec les médicaments utilisés concomitamment. Il importe que la finérénone soit utilisée uniquement dans l'indication qui lui a été octroyée et moyennant la surveillance étroite de la kaliémie. (mars 2023)(55)

  / Finerenon: Hyperkaliëmie blijft een grote bezorgdheid bij gebruik van mineralocorticoïdreceptor-antagonisten, zeker bij patiënten met nierinsufficiëntie. Hoewel de onderzoekers claimen dat finerenon minder vaak hyperkaliëmie zou geven dan spironolacton of eplerenon, zijn hierover weinig gegevens uit klinische studies beschikbaar. Het risico van hyperkaliëmie kan nog verder toenemen door mogelijke interacties met gelijktijdig gebruikte geneesmiddelen. Het zal belangrijk zijn dat finerenon enkel binnen de toegekende indicatie gebruikt wordt en onder nauwe monitoring van de kaliëmie. (maart 2023)(56)

11.1.4 ACE-inhibitors

11.1.4.1 Contraindications (among the selected comorbidities of HF)

- Fosinopril: insuffisance rénale sévère (RCP). (7)/ Fosinopril: ernstige nierinsufficiëntie (SKP). (7)

11.1.4.2 Interactions (with drugs used in the comorbidities selected in HF)

- Baisse excessive de la pression artérielle, surtout orthostatique, en cas d'administration concomitante e.a. d'inhibiteurs de la phosphodiestérase de type 5. (7) / Overdreven bloeddrukdaling, vooral orthostatisch, bij combineren van meerdere antihypertensiva, bij associëren met o.a. fosfodiësterase type 5-inhibitoren. (7)
- Suspicion d'un risque accru d'hypoglycémie chez les patients sous antidiabétiques. (7) / Vermoeden van verhoogd risico van hypoglykemische aanvallen bij patiënten op antidiabetica. (7)
- Risque accru d'angiœdème en cas d'utilisation concomitante d'autres médicaments susceptibles de provoquer un angiœdème comme le complexe sacubitril/valsartan, et la vildagliptine (et peut-être aussi les autres gliptines) (7) /
  Verhoogd risico op angio-oedeem bij gelijktijdig gebruik van andere geneesmiddelen die angio-oedeem kunnen veroorzaken: sacubitril/valsartan complex, racecadotril, everolimus, sirolimus en temsirolimus, estramustine en vildagliptine (en mogelijk ook de andere gliptines). (7)

11.1.4.3 Special precautions and monitoring in cases of comorbidity

- Détérioration de la fonction rénale (et parfois insuffisance rénale aiguë), surtout chez les patients atteints d'une affection rénale préexistante, chez les patients atteints d'insuffisance cardiaque et en cas d'hypovolémie prononcée ou de déshydratation(7). / Verslechtering van de nierfunctie (en soms acute nierinsufficiëntie), vooral bij patiënten met voorafbestaand nierlijden en bij patiënten met hartfalen, uitgesproken volumedepletie of dehydratie. (7).
- in patients with reduced renal perfusion, glomerular filtration rate may be critically dependent on the renin-angiotensin-aldosterone system and the use of ACE inhibitors may provoke problems. (8)
- Augmentation du risque de détérioration de la fonction rénale particulièrement en cas de traitement concomitant par un IECA + AINS + diurétique. (7) / Verdere verslechtering van de nierfunctie, zeker bij combineren van een ACE-inhibitor + een NSAID + een diureticum. (7)
- En cas d'insuffisance rénale : risque particulièrement accru d'hyperkaliémie, surtout en cas d'association à d'autres médicaments épargneurs de potassium (notamment suppléments de potassium, des diurétiques d'épargne potassique, des sartans, triméthoprime (co-trimoxazole), héparines et AINS). (7) / Verhoogd risico van hyperkaliëmie bij associëren met andere kaliumsparende middelen (o.a. kaliumsupplementen (ook dieetzouten), kaliumsparende diuretica, sartanen, trimethoprim (co-trimoxazol), heparines en NSAID's); dit risico is vooral hoog bij bestaan van nierinsufficiëntie. (7)
- Moderate impairment of renal function either before or during use of ACE inhibitors is not necessarily an indication to stop therapy. The effects of ACE inhibitors on renal function are generally reversible, and the reduction in filtration pressure may result in renoprotection. (8)
- Patients with existing renal disease or taking high doses should be monitored regularly for proteinuria. (8)

11.1.5 Sartans

11.1.5.1 Interactions (with drugs used in the comorbidities selected in HF)

- Baisse excessive de la pression artérielle, surtout orthostatique, en cas d'administration concomitante e.a. d'inhibiteurs de la phosphodiestérase de type 5. (7) / Overdreven bloeddrukdaling, vooral orthostatisch, bij combineren van meerdere antihypertensiva, bij associëren met o.a. fosfodiësterase type 5-inhibitoren. (7)

11.1.5.2 Special precautions and monitoring in cases of comorbidity

- En cas d'insuffisance rénale : risque particulièrement accru d'hyperkaliémie, surtout en cas d'association à d'autres médicaments épargneurs de potassium (notamment suppléments de potassium, des diurétiques d'épargne potassique, des sartans, triméthoprime (co-trimoxazole), héparines et AINS). (7) / Verhoogd risico van hyperkaliëmie bij associëren met andere kaliumsparende middelen (o.a. kaliumsupplementen (ook dieetzouten), kaliumsparende diuretica, sartanen, trimethoprim (co-trimoxazol), heparines en NSAID's); dit risico is vooral hoog bij bestaan van nierinsufficiëntie.(7)
- Since hyperkalaemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment, and potassium-sparing diuretics should generally be avoided. (8)

11.1.6 Sacubitril/valsartan

11.1.6.1 Interactions (with drugs used in the comorbidities selected in HF)

- Baisse excessive de la pression artérielle, surtout orthostatique, en cas d'administration concomitante e.a. d'inhibiteurs de la phosphodiestérase de type 5. (7) / Overdreven bloeddrukdaling, vooral orthostatisch, bij combineren van meerdere antihypertensiva, bij associëren met o.a. fosfodiësterase type 5-inhibitoren. (7)

11.1.6.2 Special precautions and monitoring in cases of comorbidity

- L'utilisation concomitante d'aliskirène est déconseillée et est contre-indiquée en cas de diabète ou d'insuffisance rénale. (folia décembre 2016 (info recentes))(57) / Gelijktijdig gebruik van aliskiren wordt afgeraden, en is gecontra-indiceerd in geval van diabetes of nierinsufficiëntie. (58)
- En cas d'insuffisance rénale : risque particulièrement accru d'hyperkaliémie, surtout en cas d'association à d'autres médicaments épargneurs de potassium (notamment suppléments de potassium, des diurétiques d'épargne potassique, des sartans, triméthoprime (co-trimoxazole), héparines et AINS). (7) / Verhoogd risico van hyperkaliëmie bij associëren met andere kaliumsparende middelen (o.a. kaliumsupplementen (ook dieetzouten), kaliumsparende diuretica, sartanen, trimethoprim (co-trimoxazol), heparines en NSAID's); dit risico is vooral hoog bij bestaan van nierinsufficiëntie(7)
- Since hyperkalaemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment, and potassium-sparing diuretics should generally be avoided. (8)

11.1.7 β-blockers

- Il y a des bénéfices prouvés en termes de morbidité et de mortalité cardio-vasculaires pour le bisoprolol, le carvédilol, le métoprolol succinate et le nébivolol. Parmi ceux -ci, le bisoprolol, le métoprolol, le nébivolol sont cardiosélectifs (β_1). (7) / Winst op cardiovasculaire morbiditeit en mortaliteit bewezen voor bisoprolol, carvedilol, metoprololsuccinaat en nebivolol. (7)

11.1.7.1 Contraindications (with HF or among the selected comorbidities of HF)

- La BPCO est une contre-indication relative pour les β-bloquants non cardiosélectifs. (7) / COPD is een relatieve contra-indicatie voor de niet-cardioselectieve β-blokkers (7)
- Insuffisance cardiaque aiguë ou insuffisamment contrôlée. (7) / Acuut of onvoldoende gecontroleerd hartfalen. (7)
- L'utilisation de vérapamil par voie intraveineuse est contre-indiquée chez les patients sous β-bloquants en raison du risque d'insuffisance cardiaque, de bloc AV complet et de choc. Pour la même raison, l'administration intraveineuse de β-bloquants est contre-indiquée en cas d'utilisation chronique de vérapamil. (7) / Het gebruik van verapamil intraveneus is gecontra-indiceerd bij patiënten onder β-blokkers wegens het gevaar voor hartfalen, volledig AV-blok en shock. Dit geldt ook voor de toediening van intraveneuze β-blokkers bij chronisch gebruik van verapamil. (7)

11.1.7.2 Interactions (with drugs used in HF or in the comorbidities selected in HF)

- Baisse excessive de la pression artérielle, surtout orthostatique, en cas d'administration concomitante e.a. d'inhibiteurs de la phosphodiestérase de type 5(7). / Overdreven bloeddrukdaling, vooral orthostatisch, bij combineren van meerdere antihypertensiva, bij associëren met o.a. fosfodiësterase type 5-inhibitoren. (7)
- In diabetic patients beta blockers can reduce the response to insulin and oral hypoglycaemics through their effects on pancreatic beta receptors. (8)
- Aggravation des épisodes d'hypoglycémie chez les patients sous antidiabétiques, et les symptômes d'hypoglycémie peuvent être masqués (moins avec les β-bloquants cardiosélectifs). (7) / Verergeren van de hypoglykemische aanvallen bij patiënten op antidiabetica, en maskeren van de symptomen van hypoglykemie (minder met cardioselectieve β-blokkers). (7)
- Beta blockers can inhibit the normal physiological response to hypoglycaemia and mask the typical sympathetic warning signs. (8)
- Diminution de l'effet des β2-mimétiques dans l'asthme et la BPCO en particulier par les β-bloquants non sélectifs. (7) / Vermindering van het effect van β2-mimetica bij astma en COPD: zeker door de niet-selectieve β-blokkers. (7)
- Risque accru d'effets indésirables des β-bloquants (bradycardie, bloc auriculo-ventriculaire et diminution de la contractilité myocardique) en cas d'association au vérapamil, dans une moindre mesure, en cas d'association au diltiazem, ou en cas d'utilisation concomitante d'antiarythmiques. L'utilisation de vérapamil par voie intraveineuse est contre-indiquée chez les patients sous β-bloquants en raison du risque d'insuffisance cardiaque, de bloc AV complet et de choc. Pour la même raison, l'administration intraveineuse de β-bloquants est contre-indiquée en cas d'utilisation chronique de vérapamil. (7) / Verhoogd risico van ongewenste effecten van β-blokkers (bradycardie, atrioventriculair blok en verminderde myocardcontractiliteit) bij associëren met verapamil, in mindere mate met diltiazem, en met antiaritmica. Het gebruik van verapamil intraveneus is gecontra-indiceerd bij patiënten onder

β-blokkers wegens het gevaar voor hartfalen, volledig AV-blok en shock. Dit geldt ook voor de toediening van intraveneuze β-blokkers bij chronisch gebruik van verapamil. (7)
- Risque accru de bradycardie en cas d'association à l'ivabradine. (7) / Verhoogd risico van bradycardie bij associëren met ivabradine. (7)

11.1.7.3 Special precautions and monitoring in cases of HF or associated comorbidity

- The sympathetic nervous system is involved in the control of carbohydrate metabolism and beta blockers can interfere with carbohydrate and insulin regulation; both hypoglycaemia and hyperglycaemia have been reported in patients with no history of diabetes, as well as in patients with types 1 or 2 diabetes mellitus. (8)
  Risque d'augmentation de la résistance à l'insuline, avec élévation de la glycémie et hypertriglycéridémie. Il n'est pas clair quelle en est la pertinence clinique à long terme étant donné que, malgré ces effets, les β-bloquants finissent par induire une diminution de la mortalité et de la morbidité cardio-vasculaires, même chez les patients diabétiques. (7) / Toename van de insulineresistentie met verhogen van de glykemie en hypertriglyceridemie. De klinische relevantie hiervan op lange termijn is onduidelijk aangezien, ondanks deze effecten, met β-blokkers toch een daling van de cardiovasculaire mortaliteit en morbiditeit bekomen wordt, ook bij diabetici. (7)
- Les β-bloquants cardiosélectifs peuvent être utilisés chez des patients atteints de BPCO et éventuellement chez des patients atteints d'asthme léger à modérément sévère s'il existe une indication évidente; il convient toutefois d'être attentif à l'apparition d'un bronchospasme lors de la prise de la première dose. (7) / Cardioselectieve β-blokkers kunnen gebruikt worden bij patiënten met COPD en eventueel bij patiënten met mild tot matig ernstig astma indien er een duidelijke indicatie is; wel moet er aandacht zijn voor optreden van bronchospasme bij inname van de eerste dosis. (7)

11.1.8 SGLT-2 inhibitors

see diabetes

11.1.9 Digitalis glycosides (Digoxin)

11.1.9.1 Contra-indication (with HF or associated comorbidities)

- Fibrillation auriculaire et flutter auriculaire avec rythme ventriculaire lent. (7) /Voorkamerfibrillatie en -flutter met traag ventriculair ritme. (7)
- Insuffisance rénale sévère (RCP). (7) / Ernstige nierinsufficiëntie (SKP). (7)

11.1.9.2 Interactions (with HF drugs or with drugs used in the comorbidities selected in HF)

- Augmentation de la sensibilité aux glycosides digitaliques par des médicaments diminuant la kaliémie (p.ex. diurétiques augmentant la perte de potassium, corticostéroïdes). (7) / Verhoogde gevoeligheid voor digitalisglycosiden door geneesmiddelen die de kaliëmie verlagen (bv. kaliumverliezende diuretica, corticosteroïden). (7)
- Hypokalaemia predisposes to digoxin toxicity; adverse reactions to digoxin may be precipitated if hypokalaemia occurs, for example after prolonged use of diuretics. Thiazides and loop diuretics cause hypokalaemia and also hypomagnesaemia which may lead to

cardiac arrhythmias. Other causes of hypokalaemia include treatment with beta2 agonists (such as salbutamol), amphotericin. (8)

- Serum-digoxin concentrations may be significantly increased by amiodarone and reduction of digoxin dosage may be required. (8)
- Other antiarrhythmics may have additive effects on the myocardium increasing the likelihood of adverse effects(8)
- Beta blockers may potentiate bradycardia due to digoxin. (8)
- Calcium-channel blockers may increase digoxin concentrations. (8)

11.1.9.3 Special precautions and monitoring in cases of HF or associated comorbidity

- Almost any deterioration in the condition of the heart or circulation may increase the sensitivity to digoxin. (8)
- La détermination des concentrations plasmatiques de la digoxine (recommandations actuelles: de préférence entre 0,5 et 0,9 ng/ml, ne dépassant pas 1,2 ng/ml) est indiquée, en particulier chez les patients en insuffisance rénale. (7) / Meten van de plasmaconcentraties van digoxine (huidige adviezen: bij voorkeur tussen 0,5 en 0,9 ng/ml, niet boven 1,2 ng/ml) is aangewezen, zeker bij patiënten met nierinsufficiëntie. (7)
- En cas d'insuffisance rénale, les doses doivent être réduites. Chez les personnes âgées, la fonction rénale est toujours altérée, et la dose doit être réduite dans tous les cas. (7) / Bij nierinsufficiëntie moeten de doses verminderd worden. Bij ouderen is de nierfunctie steeds verminderd, en dient de dosis in elk geval gereduceerd te worden. (7)

11.1.10 Dobutamine

11.1.10.1 Special precautions and monitoring in cases of comorbidity

- La prudence s'impose e.a. chez les patients présentant une affection cardio-vasculaire (e.a. arythmies cardiaques) ou les diabétiques. (7) / Voorzichtigheid is geboden bij patiënten met cardiovasculair lijden (in het bijzonder hartaritmieën, ischemisch hartlijden, hypertensie), patiënten met hyperthyreoïdie, diabetici en ouderen. (7)

11.1.11 Ivabradine

11.1.11.1 Contraindications (among the selected comorbidities of HF)

- Utilisation simultanée du diltiazem ou du vérapamil. (7) / Gelijktijdig gebruik van diltiazem of verapamil. (7)

11.1.11.2 Interactions (with drugs used in the comorbidities selected in HF)

- Risque de bradycardie sévère en cas d'association avec e.a. des β-bloquants, le vérapamil ou le diltiazem. (7) / Risico van te sterke daling van de hartfrequentie bij combinatie met β-blokkers, verapamil of diltiazem. (7)

11.1.11.3 Special precautions and monitoring in cases of comorbidity

- Ivabradine is not recommended in atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function, and regular monitoring for such arrhythmias should be performed. If resting heart rate falls below 50 beats/minute the dose should be reduced; treatment should be stopped if this rate persists. (8)
- Ivabradine should be used with caution in severe renal impairment (creatinine clearance of less than 15 mL/minute). (8)

11.1.12 Levosimendan

11.1.12.1 Contra-indications (among the selected comorbidities of HF)

- Insuffisance rénale sévère (RCP) (7) / Ernstige nierinsufficiëntie; ernstige leverinsufficiëntie (SKP). (7)

11.1.13 Milrinone

11.1.13.1 Special precautions and monitoring in cases of comorbidity

- Des effets indésirables rares sont e.a. la fibrillation ventriculaire ou un bronchospasme. (7)/ Zeldzame bijwerkingen zijn o.a. ventrikelfibrilleren of bronchospasme. (7)

11.1.14 Nitrate derivatives

11.1.14.1 Interactions (with drugs used in the comorbidities selected in HF)

- Hypotension sévère en cas d'association à un inhibiteur de la phosphodiestérase de type 5 ou au riociguat. (7) / Ernstige hypotensie bij associëren met een fosfodiësterase type 5-inhibitor (zie 7.3.1. Fosfodiësterase type 5-inhibitoren) of riociguat (zie 1.13. Middelen bij pulmonale hypertensie). (7)

11.1.15 Vericiguat

11.1.15.1 Contra-indications (among the selected comorbidities of HF)

- Association à d'autres inducteurs de la guanylate cyclase soluble dont fait partie le riociguat. (7) /Associatie met andere inductoren van het oplosbaar guanyaatcyclase. (7)

11.2 Drugs used in type 2 diabetes

11.2.1 Insulins

11.2.1.1 Interactions (with drugs used in heart failure)

- Risque accru d'hypoglycémie en cas d'association avec des β-bloquants (+ diminution des symptômes subjectifs de l'hypoglycémie) et possible aussi avec les IECA. (7) / Verhoogd risico van hypoglykemie en vermindering van de subjectieve symptomen van hypoglykemie bij associëren met β-blokkers(+ afname van subjectieve symptomen van hypoglykemie). Mogelijk verhoogd risico van hypoglykemie bij associëren met ACE-inhibitoren. (7)
- Beta blockers can inhibit the normal physiological response to hypoglycaemia and mask the typical sympathetic warning signs. (8)
- ACE inhibitors, beta blockers (which may also mask the warning signs of hypoglycaemia) may decrease insulin requirements. (8)
- Risque accru d'insuffisance cardiaque avec la pioglitazone en cas d'association avec l'insuline. (7) / Verhoogd risico van hartfalen door pioglitazon bij associëren met insuline. (7)

11.2.2 Metformin

11.2.2.1 Contra-indication (with HF)

- Présence de facteurs de risque d'acidose lactique (*voir "Précautions particulières"*).(7) / Aanwezigheid van risicofactoren voor optreden van melkzuuracidose (zie rubriek "Bijzondere voorzorgen").(7)
- Metformin has been contra-indicated in diabetic patients with heart failure, because of an increased risk of lactic acidosis(8). L'incidence de l'acidose lactique chez les patients diabétiques est cependant faible (0,03 cas /1.000 patients/an) et assez comparable chez les patients traités ou non par la metformine.(folia dec 2008). (59) / De incidentie van melkzuuracidose bij diabetici is echter gering (0,03 gevallen/1.000 patiënten/jaar) en nogal vergelijkbaar voor patiënten al dan niet behandeld met metformine.(60)
- Des données provenant de méta-analyses et d'études prospectives indiquent que les avantages de la metformine(59) [with lower rates of morbidity and mortality, of any cause, in patients with heart failure (8)] contrebalancent le plus souvent le risque d'acidose lactique. (59)/ Gegevens uit meta-analyses en prospectieve studies wijzen er inderdaad op dat in deze situaties de voordelen van metformine [with lower rates of morbidity and mortality, of any cause, in patients with heart failure (8)] meestal opwegen tegen het risico van melkzuuracidose. (60)
- Ainsi, l' *insuffisance cardiaque stable* (NYHA I et II) e.a. ne devraient plus être considérés comme une contre-indication absolue(59)./ Stabiel hartfalen (NYHA I en II) zouden dan ook niet meer mogen beschouwd worden als absolute contra- indicaties. (60) It has been suggested that metformin may be used, with caution, in diabetic patients with compensated, stable heart failure. However, it is still contra-indicated in those with acute or unstable symptoms and in those with coexisting risk factors such as renal impairment. (8)
- Remarque : contre-indication selon RCP : Maladie aiguë ou chronique pouvant entraîner une hypoxie tissulaire, telle que: insuffisance cardiaque e.a. (7) / Opmerking : contra-indicatie volgens de SKP : Acute of chronische aandoeningen die weefselhypoxie kunnen veroorzaken, zoals: o.a. hartfalen. (7)

11.2.2.2 Special precautions and monitoring in HF

- Conditions associated with hypoxia, such as acute heart failure a.o. may increase the risk of lactic acidosis. (8)
- Le plus grand risque d'acidose lactique survient chez les patients précaires (personnes âgées ou patients présentant une décompensation cardiaque ou une BPCO), en cas de diminution soudaine de la fonction rénale due à la déshydratation, en particulier si en association avec des AINS et/ou des IECA ou des sartans. Cela peut être prévenu en réduisant la dose ou en arrêtant temporairement la metformine en cas de déshydratation. (7) / Het grootste risico op melkzuuracidose treedt op bij kwetsbare patiënten (ouderen of patiënten met hartdecompensatie of COPD) in geval van plotse vermindering van de nierfunctie door dehydratie, zeker bij gelijktijdig gebruik met NSAID's en/of ACE-inhibitoren of sartanen. Dit kan voorkomen worden door de dosis te verminderen of tijdelijk metformine te staken bij dehydratie. (7)
- Les patients atteints d'insuffisance rénale doivent être informés d'arrêter immédiatement la metformine en cas de vomissements et de diarrhée. (7) / Patiënten met verminderde nierfunctie moeten geïnstrueerd worden hun metformine direct te stoppen bij braken en diarree. (7)

11.2.3 Sulfonylureas

11.2.3.1 Interactions (with drugs used in heart failure)

- Risque accru d'hypoglycémie en cas d'association e.a. avec des β-bloquants (+ diminution des symptômes subjectifs de l'hypoglycémie) et les IECA. (7) / Verhoogd risico van hypoglykemie en vermindering van de subjectieve symptomen van hypoglykemie bij associëren met β-blokkers en ACE-inhibitoren. (7)
- Beta blockers can inhibit the normal physiological response to hypoglycaemia and mask the typical sympathetic warning signs. (8)
- Beta blockers may reduce the efficacy of sulfonylureas by impairing the release of insulin from the pancreas; cardioselective beta blockers may have less of an effect than non-selective ones. (8)

11.2.4 Glinides

11.2.4.1 Interactions (with drugs used in heart failure)

- Risque accru d'hypoglycémie en cas d'association e.a. avec des β-bloquants (+ diminution des symptômes subjectifs de l'hypoglycémie) et les IECA. (7) / Verhoogd risico van hypoglykemie en vermindering van de subjectieve symptomen van hypoglykemie bij associëren met β-blokkers en ACE-inhibitoren. (7)

11.2.5 Glitazones

11.2.5.1 Contraindications (with heart failure)

- Insuffisance cardiaque ou antécédents. (7) / Hartfalen of antecedenten ervan. (7)
- Les effets indésirables sont e.a. rétention hydrosodée avec risque de déclencher ou d'aggraver une insuffisance cardiaque. Il existe également un risque accru d'insuffisance cardiaque en cas d'utilisation concomitante d'insuline ou d'AINS. (7) / Bijwerkingen zijn onder andere water- en zoutretentie, met mogelijk uitlokken of verergeren van hartfalen. Er is ook een verhoogd risico van hartfalen bij associëren met insuline en met NSAID's. (7)

11.2.5.2 Special precautions and monitoring in HF

- Chez les patients avec des facteurs de risque d'insuffisance cardiaque, la prudence est de rigueur: une instauration progressive du traitement, une adaptation lente de la dose et une surveillance étroite sont recommandées. (7) / Bij patiënten met risicofactoren voor hartfalen is voorzichtigheid geboden: traag opstarten en aanpassen van de dosis en nauwgezette monitoring worden aangeraden. (7)

11.2.6 GLP-1 agonists

No relevant information found.

11.2.7 Gliptins (DPP-4-inhibitors)

11.2.7.1 Interactions (with drugs used in heart failure)

- The efficacy of sitagliptin may be affected by other drugs that have an independent effect on blood glucose. (8)

- La vildagliptine (et probablement les autres gliptines également) augmente le risque d'angioœdème en cas d'usage concomitant avec des IECA. (7) / Vildagliptine (en waarschijnlijk ook met de andere gliptinen): verhoogd risico op angioedeem bij gelijktijdig gebruik met ACE-inhibitoren. (7)

11.2.7.2 Special precautions and monitoring in HF

- Il existe une possible augmentation du risque d'insuffisance cardiaque. Prudence en cas d'insuffisance cardiaque (7) / Er is een mogelijk verhoogd risico van hartfalen. Voorzichtigheid is geboden bij patiënten met hartfalen. (7)

11.2.8 Gliflozines (SGLT2 inhibitors)

11.2.8.1 Interactions (with HF drugs or with drugs used in the comorbidities selected in HF)

- Hypoglycémie en cas d'association à un sulfamidé hypoglycémiant, à un glinide ou à l'insuline. (7) / Hypoglykemie bij associatie met een hypoglykemiërend sulfamide, een glinide of insuline. (7)
- En raison du risque accru d'hypoglycémie en cas d'association à un sulfamidé hypoglycémiant et/ou à une insuline basale, une réduction de la dose du sulfamidé hypoglycémiant et/ou de l'insuline est conseillée. (7) / Wegens het verhoogde risico op hypoglykemie in combinatie met een hypoglykemiërend sulfamide en/of insuline wordt geadviseerd de dosis van de hypoglykemiërend sulfamide en/of insuline te verlagen. (7)
- Augmentation de l'effet des thiazides et des diurétiques de l'anse. (7) / Toename van het effect van thiaziden en lisdiuretica. (7)

11.2.8.2 Special precautions and monitoring in heart failure or associated comorbidity

- L'efficacité hypoglycémiante des gliflozines diminue lorsque la clairance rénale de créatinine est inférieure à 60 ml/min. (7) / Het hypoglykemiërend effect van gliflozinen neemt af wanneer de renale creatinineklaring lager is dan 60 ml/min. (7)
- Il est nécessaire de contrôler la fonction rénale avant l'instauration du traitement et régulièrement par la suite. (7) /De nierfunctie controleren voor de start van de behandeling en nadien op regelmatige tijdstippen. (7)
- The efficacy of SGLT2 inhibitors is dependent on renal function and reduced efficacy is expected in patients with moderate to severe renal impairment. Additionally, exposure is increased leading to an increased incidence of renal adverse effects and adverse effects relating to volume depletion. Although no dose adjustment of dapagliflozin is recommended in those with mild renal impairment, its use is not recommended in moderate to severe impairment (creatinine clearance < 60 mL/min). Renal function should be checked before starting dapagliflozin and monitored during treatment. (8)
- Prudence chez les patients qui présentent un risque d'hypovolémie tels que les patients sous diurétiques ou les personnes âgées. Lors d'épisodes aigus de déshydratation (diarrhée, vomissements, fièvre,...) qui durent plus de 24 heures, il faut envisager une réduction de la dose ou l'arrêt temporaire de la gliflozine pour éviter une atteinte rénale aiguë, en particulier chez les patients âgés ou vulnérables. (7) / Voorzichtigheid bij patiënten met risico van volumedepletie zoals patiënten onder diuretica, ouderen. Tijdens acute episodes van dehydratie (diarree, braken, koorts,…) die langer dan 24u aanhouden, moet overwogen worden tijdelijk de dosis van de gliflozinen te verlagen of de inname stop te zetten om acute nierschade te voorkomen, zeker bij oudere of kwetsbare patiënten. (7)
- Les effets indésirables sont parfois: Insuffisance rénale aigue, transitoire. (7) /Bijwerkingen zijn soms: acute nierinsufficiëntie, van voorbijgaande aard. (7)

11.3 Drugs used in morbid obesity

11.3.1 Orlistat

No relevant information found.

11.3.2 Liraglutide

No relevant information found.

11.3.3 Naltrexon + bupropion

No relevant information found.

11.4 Drugs used in COPD

11.4.1 β2-agonists

11.4.1.1 Interactions (with drugs used in heart failure)

- Diminution de l'effet des β2-mimétiques en cas d'association à des β-bloquants (en particulier les non sélectifs). (7) / Verminderd effect van β2-mimetica bij associëren met β-blokkers (zeker de niet-selectieve). (7)
- Non-cardioselective beta blockers oppose the bronchodilator effects of beta-agonist bronchodilators. No adverse interaction normally occurs between beta-agonist bronchodilators and cardioselective beta blockers. (8)
- Risque accru d'hypokaliémie en cas de prise concomitante de médicaments provoquant une hypokaliémie, p.ex. des diurétiques. (7) / Verhoogd risico van hypokaliëmie bij gelijktijdig gebruik van middelen die hypokaliëmie uitlokken, bv. Diuretica. (7)
- The arrhythmogenic potential of this interaction may be clinically important in patients with ischaemic heart disease. (8)
- Hypokalaemia produced by beta2 agonists may result in an increased susceptibility to digitalis-induced arrhythmias although salbutamol intravenously and orally can also decrease serum concentrations of digoxin (8)

11.4.1.2 Special precautions and monitoring in heart failure

- Chez les patients atteints d'une affection cardio-vasculaire instable (p.ex insuffisance cardiaque sévère), les β2-mimétiques doivent être utilisés avec prudence. (7) / Bij patiënten met instabiel cardiovasculair lijden (bv. recent myocardinfarct, levensbedreigende hartaritmieën, ernstig hartfalen) dienen β2-mimetica voorzichtig te worden gebruikt. (7)
- A meta-analysis of randomised, placebo-controlled studies in patients with asthma or chronic obstructive pulmonary disease (COPD) confirmed that single doses of beta2 agonists can cause an increase in heart rate and a reduction in potassium concentrations. The longer-term effects of beta2 agonists on the cardiovascular system were also assessed and an increased risk of adverse cardiovascular events due to sinus tachycardia was found. There was also a trend towards an increase in major adverse events including ventricular tachycardia, atrial fibrillation, heart failure, myocardial infarction, cardiac arrest, and sudden death. (8)

11.4.2 Anticholinergics

11.4.2.1 Special precautions and monitoring in heart failure

- Chez les patients atteints d'une affection cardio-vasculaire instable (p.ex. insuffisance cardiaque sévère), les anticholinergiques doivent être utilisés avec prudence. (7) / Bij patiënten met instabiel cardiovasculair lijden (bv. recent myocardinfarct, levensbedreigende hartaritmieën, ernstig hartfalen) dienen anticholinergica voorzichtig te worden gebruikt . (7)
- La possibilité d'effets indésirables cardiaques graves dus aux LAMA reste controversée mais les données récentes sont rassurantes; néanmoins il persiste une suspicion d'événements cardiovasculaires en début de traitement. (7) / De mogelijkheid van ernstige cardiale ongewenste effecten door LAMA's blijft controversieel maar recente gegevens zijn geruststellend; er bestaat echter nog steeds een vermoeden van cardiovasculaire events bij het begin van de behandeling.

11.4.3 Theophylline

11.4.3.1 Interactions (with drugs used in heart failure)

- Xanthines can potentiate hypokalaemia caused by hypoxia or associated with the use of diuretics a.o. (8)
- The interaction between theophylline and beta blockers is complex. In general, however, beta blockers should be avoided in patients taking theophylline as they can dangerously exacerbate bronchospasm in patients with a history of asthma or chronic obstructive pulmonary disease(8)

11.4.3.2 Special precautions and monitoring in heart failure

- The possibility that adverse effects such as hypokalaemia may be potentiated if theophylline is given with diuretics should be borne in mind. (8)
- La prudence s'impose e.a. chez les patients présentant des arythmies ou d'autres maladies cardiaques et chez les patients présentant un risque d'hypokaliémie. (7) / Voorzichtigheid is geboden o.a. bij patiënten met hartaritmieën of andere cardiale aandoeningen, hypertensie, epilepsie, hyperthyreoïdie, ulcus pepticum, of risico van hypokaliëmie. (7)

- En cas d'insuffisance cardiaque e.a., les doses doivent être réduites. (7) / Bij hart-insufficiëntie moet de dosis gereduceerd worden. (7)

11.4.4 Corticosteroids

- Des effets indésirables systémiques sont fréquents en cas d'utilisations répétées in situ (p.ex. intra-articulaires) et peuvent également survenir en cas d'application prolongée de doses élevées de corticostéroïdes au niveau de la peau ou des muqueuses, et en cas d'inhalation. (7) / Systemische bijwerkingen komen vaak voor bij herhaald gebruik in situ (bijv. intra-articulair) en kunnen ook optreden bij langdurige toepassing van hoge doses corticosteroïden op de huid of slijmvliezen en bij inhalatie. (7)

11.4.4.1 Interactions (with drugs used in heart failure)

- Augmentation du risque d'hypokaliémie en cas d'association à d'autres médicaments provoquant une hypokaliémie (p.ex. diurétique augmentant la perte de potassium). (7) / Verhoogd risico van hypokaliëmie bij associëren met andere geneesmiddelen die hypokaliëmie veroorzaken (bv. kaliumverliezende diuretica). (7)

11.4.4.2 Special precautions and monitoring in heart failure

- Systemic corticosteroids should be used with great caution in the presence of heart failure, Cohort studies established that oral glucocorticoid use was associated with an increased risk for heart failure, and that high-dose therapy was associated with an increased risk for cardiovascular disease, including myocardial infarction. (8)

11.5 Drugs used in pulmonary hypertension

11.5.1 Endothelin receptor agonists (ambrisentan, bosentan and macitentan)

No relevant information found.

11.5.2 Phosphodiesterase-5 inhibitors (sildenafil and tadalafil)

11.5.2.1 Interactions (with drugs used in heart failure)

- Utilisation concomitante de dérivés nitrés e.a. (risque d'hypotension sévère) est contre-indiquée. (aussi riociguat, molsidomine, alpha-bloquants) (7) / Gebruik samen met nitraten o.a. (risico van ernstige hypotensie) is gecontra-indiceerd. (ook riociguat, molsidomine, alfablokkers). (7)

11.5.3 Epoprostenol

No relevant information found.

11.5.4 Riociguat

11.5.4.1 Interactions (with drugs used in heart failure)

- Utilisation concomitante de dérivés nitrés e.a. est contre -indiquée en raison du risque accru d'hypotension. (aussi inhibiteur de phosphodiestérase de type 5) (7) / Gelijktijdig gebruik van nitraten e.a. is gecontra-indiceerd vanwege het verhoogde risico op hypotensie. (7)

11.5.5 Selexipag

11.5.5.1 Contra-indication (with HF)

- Insuffisance cardiaque(7) / Hartfalen(7)

11.5.6 Treprostinil

11.5.6.1 Contra-indication (with HF)

- Insuffisance cardiaque (RCP) (7) / Hartfalen (SKP) (7)

11.6 Drugs used in chronic kidney disease

11.6.1 Finerenone

See mineralocorticoid receptor antagonist

11.6.2 Gliflozines (SGLT-2 inhibitors)

See in drugs used in diabetes

11.7 Drugs used in atrial fibrillation

11.7.1 β-blockers

see in drugs used in HF

11.7.2 Verapamil and diltiazem

11.7.2.1 Contra-indication (with HF)

- Insuffisance cardiaque. (7) / Hartfalen (7)
- Adverse effects or verapamil on the heart include a.o. worsening heart failure. Diltiazem has been associated with the development of heart failure and great care is required in patients with impaired left ventricular function. (8)
- L'utilisation de vérapamil par voie intraveineuse est contre-indiquée chez les patients sous β-bloquants en raison du risque d'insuffisance cardiaque et de choc. Ceci s'applique à l'inverse également à l'administration intraveineuse de β-bloquants en cas d'utilisation chronique de vérapamil. (7) / Het gebruik van verapamil intraveneus is gecontra-indiceerd bij patiënten onder β-blokkers, bij reciproke tachycardie bij syndroom van Wolff-Parkinson-White en bij ventrikeltachycardie, wegens het gevaar voor hartfalen en shock. (7)
- Utilisation simultanée d'ivabradine. (7) / Gelijktijdig gebruik van ivabradine. (7)

11.7.2.2 Interactions (with drugs used in heart failure)

- Risque accru d'effets indésirables des β-bloquants (bradycardie, bloc auriculo-ventriculaire et diminution de la contractilité myocardique) en cas d'association au vérapamil, et dans une moindre mesure au diltiazem. (7) /Verhoogd risico van ongewenste effecten van de β-blokkers (bradycardie, atrioventriculair blok en verminderde myocardcontractiliteit) bij associëren met verapamil en in mindere mate diltiazem. (7)
- Profound bradycardia has been reported in several patients when diltiazem was used with a beta blocker. (8)
- Baisse excessive de la pression artérielle, surtout orthostatique, e.a. en cas d'association de plusieurs antihypertenseurs, ou en cas d'administration concomitante de dérivés nitrés. (7) / Overdreven bloeddrukdaling, vooral orthostatisch, o.a. bij combineren van meerdere antihypertensiva of bij associëren met nitraten. (7)

11.7.3 Digoxin

See in HF

11.7.4 Amiodarone

11.7.4.1 Contra-indication (with HF)

- Rarely, heart failure may be precipitated or aggravated with amiodarone. (8)

11.7.4.2 Special precautions and monitoring in heart failure

- L'amiodarone peut être utilisée en présence d'une insuffisance cardiaque. (7) / Amiodaron mag gebruikt worden bij patiënten met hartfalen. (7)
- It may be used, but with caution, in patients with heart failure. (8)

11.7.5 Anticoagulants: vitamin K antagonists

11.7.5.1 Interactions (with drugs used in heart failure)

- Beta blockers, particularly those with a high lipid solubility such as propranolol, may inhibit the metabolism of warfarin. Although several studies have shown pharmacokinetic interactions between some beta blockers and oral anticoagulants, no effect on anticoagulant activity has generally been found. However, possible potentiation of the effect of warfarin by propranolol has been reported. (8)
- Chlortalidone and spironolactone have both been associated with a reduction in warfarin's activity in healthy subjects and it has been suggested that this might be a consequence of the diuresis concentrating the circulating clotting factors. (8)
- Torasemide has been reported to enhance the activity of warfarin,5 possibly by competing for metabolism through the cytochrome P450 isoenzyme CYP2C9 and by displacement of warfarin from protein-binding sites. However, bumetanide, furosemide, and the thiazides appear to have no effect on warfarin. (8)

11.7.6 DOACs

No relevant information found.

11.8 Drugs used in cachexia

11.8.1 Androgens and anabolic steroids

11.8.1.1 Special precautions and monitoring in heart failure

- La prudence s'impose si la rétention hydrosodée constitue un risque. (7) / Bij een risico op vochtretentie is voorzichtigheid geboden. (7)

11.9 Interactions with CYP isoenzymes and P-gp

The table below is adapted from the table in the “Répertoire Commenté des Médicaments” (7) and only includes medicines mentioned in the “Safety sources” section.

	Substrat de	Inhibiteur de	Inducteur de
acenocoumarol	**2C9**		

ambrisentan	2C19 3A4 P-gp		
amiodarone	**2C8 3A4**	2C9 2D6 **P-gp**	
apixaban	**3A4 P-gp**		
betamethasone	3A4		
bosentan	2C9 3A4		2C9 3A4
budesonide	3A4 P-gp		
bupropione	2B6	**2D6**	
canagliflozine	P-gp		
candesartan	2C9		
carvedilol	2C9 2D6 P-gp		
dabigatran	**P-gp**		
dexamethasone	3A4 P-gp		
digoxin	**P-gp**		
diltiazem	3A4	3A4 P-gp	
edoxaban	**P-gp**		
eplerenone	3A4		
finerenone	3A4		
fluticasone	3A4		
glibenclamide	**2C9**		

gliclazide	**2C9**
glimepiride	**2C9**
glipizide	**2C9**
gliquidone	**2C9**
hydrocortisone	3A4
indacaterol	3A4 P-gp
irbesartan	2C9
ivabradine	3A4
labetalol	2C19
linagliptin	P-gp
losartan	2C9
macitentan	3A4
methylprednisolone	3A4 P-gp
metoprolol	2D6
nebivolol	2D6
phenprocoumon	**2C9**
pioglitazone	2C8
prednisone	3A4 P-gp
prednisolone	3A4

propranolol	2D6	
repaglinide	**2C8**	
riociguat	2C8 3A4 P-pg	
rivaroxaban	**3A4 P-gp**	
salmeterol	3A4	
saxagliptin	3A4 P-gp	
selexipag	2C8	
sildenafil	3A4	
sitagliptin	3A4 P-gp	
tadalafil	3A4	
testosterone	3A4	
theophylline	**1A2**	
torasemide	2C9	
treprostinil	2C8	
valsartan	2C9	
verapamil	3A4 P-gp	3A4 **P-gp**
vilanterol	3A4 P-gp	
warfarin	**1A2 2C9**	

Liste alphabétique des substrats, inhibiteurs et inducteurs des isoenzymes CYP et P-gp /Alfabetische lijst van de substraten, inhibitoren en inductoren van CYP en P-gp

Les substrats, les inhibiteurs et les inducteurs avec lesquels on s'attend à des interactions cliniques particulièrement importantes sont indiqués en caractères gras. / De substraten, inhibitoren en inductoren waarvan men verwacht dat ze de klinisch meest relevante interacties zullen geven, zijn in vetjes aangeduid.

12 Appendix. Evidence tables.

12.1 SGLT2

12.1.1 Dapagliflozin vs placebo

12.1.1.1 DAPA-HF (HFrEF)

Ref McMurray 2019(18) Study details	**DAPA-HF trial** (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) Design: RCT ; Double-blind, parallel group Duration of follow-up: Median 18.2 months
n/population	n= 4744 randomized Mean age: -dapagliflozin: 66.2±11.0 yr -placebo: 66.5±10.8 yr Inclusion criteria Inclusion criteria included age of at least 18 years, NYHA functional classes II to IV, LVEF ≤40%, an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), and standard HF drug and device therapy.

	<u>Key exclusion criteria</u> type 1 diabetes mellitus, symptoms of hypotension or systolic blood pressure <95 mmHg, recent worsening HF or other cardiovascular events or procedures (or planned procedures), estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 (or rapidly declining renal function), and other conditions likely to prevent patient participation in the trial or greatly limit life expectancy Randomization was stratified based on type 2 diabetes diagnosis.
Intervention/comparison	dapagliflozin 10 mg vs placebo in addition to guideline directed standard of care therapy
Outcomes	**Primary outcomes:** worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **Key secondary end point** composite of HF hospitalization or cardiovascular death **Additional secondary outcomes** • total number of recurrent heart failure hospitalizations and cardiovascular deaths; • change from baseline to 8 months in the total symptom score using the Kansas City Cardiomyopathy Questionnaire (KCCQ); • the incidence of a composite worsening renal function outcome consisting of (a) ≥50% sustained decline in eGFR, or ((b) end-stage renal disease (defined as sustained eGFR <15 mL/min/1.73 m2, chronic dialysis treatment or renal transplantation) or renal death; • death from any cause
Methodology	RANDO: Adequate

	ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -dapagliflozin arm: there was incomplete follow-up for the primary endpoint in 14/2373 patients. -Placebo arm: there was incomplete follow-up for the primary endpoint in 20/2371 patients. ITT: yes (all randomized patients were included in the analyses of primary and secondary outcomes) Sponsor: AstraZeneca

12.1.1.1.1 DM

Ref Petrie 2020(19) SUBGROUP Of DAPA-HF	SUBGROUP DIABETES vs NO DIABETES <u>Prespecified:</u> Yes for **primary endpoint**, the **cardiovascular death** component of this composite, and the **first secondary outcome (**composite of HF hospitalization or cardiovascular death)

Exploratory subgroup analyses of the **primary composite endpoint** will be performed for the characteristics listed in Table 1 (which lists 14 subgroups, one of which is type 2 diabetes -T2D yes/no)

The SAP stated that the primary outcome, the cardiovascular death component of this composite, and the first secondary outcome would be analyzed in the prespecified subgroups

The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively.

Baseline characteristics
Diabetes 1983/2139 (42%)

Outcomes	
Efficacy	

worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	Overall HR 0.74 (0.65 to 0.85) P<0.001 SS SUBGROUP Diabetes HR 0.75 (0.63 to 0.90) No diabetes HR 0.73 (0.60 to 0.88) **Interaction p value**: 0.22	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
Cardiovascular death	Overall HR 0.82 (0.69 to 0.98) P NA SUBGROUP Diabetes HR 0.79 (0.63 to 1.01) No diabetes HR 0.85 (0.66 to 1.10) **Interaction p value**: 0.70	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

Cardiovascular death or hospitalization for heart failure (key secondary outcome)	Overall HR 0.75 (0.65 to 0.85) P<0.001 SUBGROUP Diabetes HR 0.75 (0.63 to 0.90) No diabetes HR 0.73 (0.60 to 0.89) **Interaction p value**: 0.83	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
No. of first and recurrent heart failure hospitalizations and cardiovascular death	Overall RR 0.75 (0.65 to 0.88) P<0.001 SUBGROUP Diabetes RR 0.77 (0.63 to 0.94) No diabetes RR 0.73 (0.59 to 0.91) **Interaction p value**: 0.74	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Worsening kidney function	Overall HR 0.71 (0.44 to 1.16) P NA SUBGROUP Diabetes HR 0.73 (0.39 to 1.34) No diabetes HR 0.67 (0.30 to 1.49) **Interaction p value**: 0.86	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Death from any cause	Overall HR 0.83 (0.71 to 0.97) P NA SUBGROUP Diabetes HR 0.78 (0.63 to 0.97) No diabetes HR 0.88 (0.70 to 1.12) **Interaction p value**: 0.45	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Change in KCCQ total symptom score at 8 mo *The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.*	<u>Overall</u> RR 1.18 (1.11 to 1.26) P<0.001 SUBGROUP <u>Diabetes</u> HR 1.22 (1.11 to 1.35) <u>No diabetes</u> HR 1.15 (1.05 to 1.26) **Interaction p value**: 0.18	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
Post hoc analysis by subgroup No significant p value for interaction for • Any serious adverse event • Discontinuation of study drug due to adverse event • Volume depletion • Kidney adverse event • Fracture • Amputation		

12.1.1.1.2 CKD

Jhund 2021(37) SUBGROUP of DAPA-HF	SUBGROUP eGFR<60mL./min/ 1.73m² vs eGFR≥60mL./min/ 1.73m² <u>Prespecified:</u> Yes for **primary endpoint**, the **cardiovascular death** component of this composite, and the **first secondary outcome (**composite of HF hospitalization or cardiovascular death) Exploratory subgroup analyses of the primary composite endpoint will be performed for the characteristics listed in Table 1 (which lists 14 subgroups, one of which is CKD yes/no) The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively. <u>Baseline characteristics</u> CKD 41% (eGFR<60 mL./min/ 1.73m²)

Outcomes	
Efficacy	

worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	Overall HR 0.74 (0.65 to 0.85) P<0.001 SS SUBGROUP CKD HR 0.72 (0.59–0.86) No CKD HR 0.76 (0.63–0.92) **Interaction p value**: 0.54	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
Cardiovascular death	Overall HR 0.82 (0.69 to 0.98) P NA SUBGROUP CKD HR 0.88 (0.69–1.13) No CKD HR 0.76 (0.59–0.98) **Interaction p value**: 0.44	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

Cardiovascular death or hospitalization for heart failure (key secondary outcome)	Overall HR 0.75 (0.65 to 0.85) P<0.001 SUBGROUP CKD HR 0.79 (0.64–0.97) No CKD HR 0.71 (0.58–0.93) **Interaction p value**: 0.50	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
Worsening kidney function (≥50% sustained decline eGFR or end-stage renal disease or renal death)	Overall HR 0.71 (0.44 to 1.16) P 0.17 SUBGROUP CKD HR 0.49 (0.23–1.06) No CKD HR 0.95 (0.50–1.82) **Interaction p value**: 0.19	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Death from any cause	Overall HR 0.83 (0.71 to 0.97) P NA SUBGROUP CKD HR 0.85 (0.68–1.07) No CKD HR 0.81 (0.64–1.02) **Interaction p value**: 0.80	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Change in KCCQ total symptom score at 8 mo *The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.*	Overall RR 1.18 (1.11 to 1.26) P<0.001 SUBGROUP CKD OR 1.13 (1.02–1.24) No CKD OR 1.17 (1.08–1.27) **Interaction p value**: 0.52	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		

No analysis of modification of effect of dapagliflozin by CKD status	

12.1.1.1.3 COPD

Dewan 2021(16) SUBGROUP of DAPA-HF	COPD status was **not** included as one of the 14 prespecified subgroups. SUBGROUP COPD vs no COPD at baseline An investigator-reported history of COPD was identified from a check box on the case report form. No specific instructions were given in relation to diagnosis of COPD. <u>Baseline characteristics</u> History of COPD 585/4744 (12.3%) Post hoc analysis

Outcomes	
Efficacy	

worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome of main trial; analysis not prespecified for this subgroup)**	Overall HR 0.74 (0.65 to 0.85) P<0.001 SS SUBGROUP Without COPD HR 0.76 (0.65–0.87) With COPD HR 0.67 (0.48–0.93) **Interaction p value**: 0.47	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Worsening HF event	Overall HR 0.70 (0.59 to 0.83) P NA SUBGROUP Without COPD HR 0.72 (0.60–0.87) With COPD HR 0.61 (0.41–0.90) **Interaction p value**: 0.42	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

First HF hospitalization	Overall HR 0.70 (0.59 to 0.83) P NA SUBGROUP Without COPD HR 0.73 (0.60–0.88) With COPD HR 0.59 (0.40–0.88) **Interaction p value**: 0.35	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
CV Death	Overall HR 0.82 (0.69 to 0.98) P NA SUBGROUP Without COPD HR 0.80 (0.66–0.97) With COPD HR 0.96 (0.61–1.51) **Interaction p value**: 0.47	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Total HF hospitalization/CV death	Overall RR 0.75 (0.65 to 0.88) P<0.001 SS SUBGROUP Without COPD RR 0.76 (0.65–0.90) With COPD RR 0.71 (0.50–1.03) **Interaction p value**: 0.71	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Death from any cause	Overall HR 0.83 (0.71 to 0.97) P NA SUBGROUP Without COPD HR 0.83 (0.69–0.99) With COPD HR 0.83 (0.57–1.22) **Interaction p value**: 0.96	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Change in KCCQ total symptom score at 8 mo	SUBGROUP Without COPD Between treatment difference 2.73 (1.47–3.99) With COPD Between treatment difference 3.42 (−0.19–7.04) **Interaction p value**: 0.71	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
AE related study drug discontinuation	Overall Dapagliflozin: 111/2368 (4.7%) Placebo: 116/2368 (4.9%) P 0.79 SUBGROUP Without COPD OR 0.98 (0.73–1.32 With COPD 0.80 (0.42–1.54) **Interaction p value**: 0.59	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Volume depletion	Overall Dapagliflozin: 178/2368 (7.5%) Placebo: 162/2368 (6.8%) P 0.40 SUBGROUP Without COPD 1.11 (0.87–1.41) With COPD 1.08 (0.59–1.97) **Interaction p value**: 0.96	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Renal AE	Overall Dapagliflozin: 153/2368 (6.5%) Placebo: 170/2368 (7.2%) P 0.36 SUBGROUP Without COPD 0.90 (0.70–1.16) With COPD 0.84 (0.50–1.42) **Interaction p value**: 0.81	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

12.1.1.1.4 BMI

McMurray 2019(18) ; Adamson 2021(48): DAPA-HF

SUBGROUP Of DAPA-HF

- SUBGROUP BMI>30 vs BMI<30
- SUBGROUP 4 BMI categories: BMI <25.0 kg/m²; BMI 25.0–29.9 kg/m²; BMI 30.0–34.9 kg/m²; BMI 35.0 -≥40 kg/m²
  (according to World Health Organization categories, namely: underweight (<18.5 kg/m²); normal weight (18.5–24.9 kg/m²); overweight (25.0–29.9 kg/m²); obesity class I (30.0–34.9 kg/m²); obesity class II (35.0–39.9 kg/m²) and obesity class III (≥40 kg/m²).)

Prespecified:

- Analysis by BMI **category <30 kg/m2 compared with ≥30 kg/m²** was a **pre-specified** subgroup analysis in DAPA-HF for the **primary endpoint,** and **the secondary composite endpoint** of CV death or HF hospitalization
- Analysis **by 4 BMI categories was not prespecified**

Other important (methodological) remarks:

- The p-values for the subgroup analyses and interaction were not adjusted for multiple comparisons
- Because of the small number of patients in the underweight category, this category was combined with the normal weight category, and obesity class II was combined with obesity class III for the same reason, in the main analysis.

Baseline characteristics

N=4744 randomized; 2 patients without recorded height, not included in analysis

BMI>30: 1672 /4742 (35.3%)

BMI <25.0 kg/m²: 1348/4742 (28.4%)
BMI 25.0–29.9 kg/m²: 1722/4742 (36.3%)
BMI 30.0–34.9 kg/m²: 1013/4742 (21.4%)
BMI 35.0 -≥40 kg/m² : 659/4742(13.9%)

Outcomes		
Efficacy		
composite outcome of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) **or death from cardiovascular causes (primary outcome)**	Overall 386/2373 vs 502/2371 HR 0.74 (0.65-0.85) p<0.001 **SS** BMI <30 259/1537 vs 320/1533 HR 0.78 (0.66-0.92) BMI ≥30 127/834 vs 182/838 HR 0.69 (0.55-0.86) **Interaction test**: not done	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
	BMI <25.0 kg/m² HR 0.74 (0.58, 0.94) BMI 25.0–29.9 kg/m2 HR 0.81 (0.65, 1.02) BMI 30.0–34.9 kg/m2 HR 0.68 (0.50, 0.92) BMI 35.0 -≥40 kg/m2 HR 0.71 (0.51, 1.00) **Interaction test**: p=0.79	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Total hospitalizations for HF and CV death (recurrent events) Adjusted for history of HF hospitalization (apart from all-cause death) and stratified by diabetes status.	Overall 567/2373 vs 742/2371 Rate ratio 0.75 (0.65-0.88) p<0.001 **SS** BMI <25.0 kg Rate ratio 0.70 (0.54, 0.91) BMI 25.0–29.9 kg/m2 Rate ratio 0.86 (0.67, 1.11) BMI 30.0–34.9 kg/m2 Rate ratio 0.75 (0.53, 1.06) BMI 35.0 -≥40 kg/m2 Rate ratio 0.67 (0.46, 0.98) **Interaction test**: p=0.63	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Change in KCCQ-TSS at 8 months (mean±SD)	Overall Difference 6.1±18.6 vs 3.3±19.2 Difference 1.18 (1.11-1.26) p<0.001 **SS** **Interaction test**: p=0.40	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Change in KCCQ-TSS at 8 months: improvement (≥5 points)	Overall: NR **Interaction test**: p=0.81	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?**

		NO **Was the test of interaction significant (interaction P <0.05)?** NO
Change in KCCQ-TSS at 8 months: deterioration (≥5 points)	Overall: NR **Interaction test**: p=0.21	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
CV death	Overall 227/2373 vs 273/2371 HR 0.82 (0.69-0.98) BMI <25.0 kg/m² HR 0.85 (0.63, 1.16) BMI 25.0–29.9 kg/m2 HR 0.94 (0.70, 1.25) BMI 30.0–34.9 kg/m2 HR 0.70 (0.46, 1.72) BMI 35.0 -≥40 kg/m2 HR 0.67 (0.41, 1.10) **Interaction test**: p=0.58	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

All-cause death	Overall 276/2373 vs 329/2371 HR 0.83 (0.71-0.97) BMI <25.0 kg/m² HR 0.81 (0.61, 1.07) BMI 25.0–29.9 kg/m2 HR 0.93 (0.71, 1.21) BMI 30.0–34.9 kg/m2 HR 0.76 (0.52, 1.10) BMI 35.0 -≥40 kg/m2 HR 0.76 (0.49, 1.17) **Interaction test**: p=0.77	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
HF Hospitalization/ urgent HF visit	Overall 237/2373 vs 326/2371 HR 0.70 (0.59-0.83) BMI <25.0 kg/m² HR 0.60 (0.44, 0.83) BMI 25.0–29.9 kg/m2 HR 0.80 (0.60, 1.06) BMI 30.0–34.9 kg/m2 HR 0.71 (0.49, 1.03) BMI 35.0 -≥40 kg/m2 HR 0.72 (0.48, 1.07) **Interaction test**: p=0.67	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
Post hoc analysis by subgroup		**Was the subgroup variable a baseline characteristic?** YES

No significant p value for interaction for • Discontinuation due to adverse event • Volume depletion • Renal adverse event • Bone fracture • Amputation • Major hypoglycaemia	**Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

12.1.1.2 DEFINE-HF (HFrEF)

Nassif 2019(20)	**DEFINE-HF trial** (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction)
Study details	Design: RCT ; Double-blind, parallel group Duration of follow-up: 12 weeks
n/population	n= 263 Mean age: 61.3y Inclusion criteria HF patients with left ventricular ejection fraction ≤40%, New York Heart Association (NYHA) class II-III, estimated glomerular filtration rate ≥30 mL/min/1.73m2 , and elevated natriuretic peptides. Exclusion criteria Recent hospitalization (within 30 days) for decompensated HF, eGFR <30 mL/min/1.73m2 at the screening visit (using modified MDRD equation), and history of type 1 diabetes mellitus Randomization was not stratified.
Intervention/comparison	dapagliflozin 10 mg vs placebo

	in addition to guideline directed standard of care therapy
Outcomes	**Dual primary outcomes:** (1) mean NT-proBNP (N-terminal pro b-type natriuretic peptide) and (2) Composite: proportion of patients with ≥5-point increase in HF disease-specific health status on the Kansas City Cardiomyopathy Questionnaire overall summary score, or a ≥20% decrease in NT-proBNP. **Key secondary end points** included proportion of patients with meaningful change in KCCQ, and NT-proBNP at each time point, mean BNP and proportion of patients with meaningful change in BNP, functional status based on 6-minute walk test, change in weight, systolic blood pressure and HbA1c. Exploratory end points included a composite of hospitalization for HF or urgent HF visits
Methodology	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -dapagliflozin arm: there was incomplete follow-up for the primary endpoint in 12/131 patients. -Placebo arm: there was incomplete follow-up for the primary endpoint in 13/132 patients. ITT: modified ITT (all randomized patients who received at least 1 dose of study medication and had at least 1 evaluable end point) Sponsor:

	AstraZeneca

12.1.1.2.1 DM

Nassif 2019(20) SUBGROUP of DEFINE-HF	For the primary end points, several subgroup analyses were prespecified, including **T2D** status, age (<65, ≥65 years), sex (male, female), race, baseline NT-proBNP (< median, ≥ median), baseline LVEF (≤30%, >30%), atrial fibrillation, baseline KCCQ-OS (<70, ≥70), baseline **eGFR** (<60, ≥60 mL/ min/1.73 m2), cause of cardiomyopathy (ischemic, non-ischemic), baseline renin angiotensin aldosterone system inhibitor type (angiotensin receptor neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, neither), baseline loop diuretic dose (furosemide equivalent mean daily dose: ≤ 40 mg, >40 mg). SUBGROUP DIABETES vs NO DIABETES Baseline characteristics Diabetes 166/263 (62%) No adjustments for multiplicity will be made for secondary and exploratory endpoints.

Outcomes	
Efficacy	

Composite: proportion of patients with ≥5-point increase in HF disease-specific health status on the **Kansas City Cardiomyopathy Questionnaire overall summary score**, or a ≥20% decrease in NT-proBNP. **(primary outcome)**	Overall adjusted OR 1.8, 95% CI 1.03–3.06 p<0.039 SS SUBGROUP Diabetes OR 1.4 (0.7 to 2.9) No diabetes OR 2.6 (0.9 to 7.4) **Interaction p value**: 0.304 NS	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
Not reported by DM subgroup		

12.1.1.2.2 CKD

Nassif 2019(20) SUBGROUP of DEFINE-HF	For the primary end points, several subgroup analyses were prespecified, including **T2D** status, age (<65, ≥65 years), sex (male, female), race, baseline NT-proBNP (< median, ≥ median), baseline LVEF (≤30%, >30%), atrial fibrillation, baseline KCCQ-OS (<70, ≥70), baseline **eGFR** (<60, ≥60 mL/ min/1.73 m2), cause of cardiomyopathy (ischemic, non-ischemic), baseline renin angiotensin aldosterone system inhibitor type (angiotensin receptor neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, neither), baseline loop diuretic dose (furosemide equivalent mean daily dose: ≤ 40 mg, >40 mg). SUBGROUP CKD (eGFR≥60) vs NO CKD (eGFR<60) Baseline characteristics eGFR (mL/min/1.73m²) dapagliflozin group 66.9 placebo group: 71.2 No adjustments for multiplicity will be made for secondary and exploratory endpoints.

Outcomes	
Efficacy	

Composite: proportion of patients with ≥5-point increase in HF disease-specific health status on the **Kansas City Cardiomyopathy Questionnaire overall summary score**, or a ≥20% decrease in NT-proBNP. **(primary outcome)**	Overall adjusted OR 1.8, 95% CI 1.03–3.06 p<0.039 SS SUBGROUP CKD OR 1.6 (0.7 to 3.9) No CKD OR 1.8(0.8 to 3.7) **Interaction p value**: 0.846 NS	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
Not reported by CKD subgroup		

12.1.1.3 DELIVER (HFpEF)

Solomon 2022(21)	**DELIVER trial** (the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure)

Study details	Design: RCT ; Double-blind, parallel group Duration of follow-up: Median 2.3 years
n/population	n= 6263 Mean age: -dapagliflozin: 71.8±9.6 yr -placebo: 71.5±9.5 yr Inclusion criteria age ≥40 years, HF diagnosis ≥6 weeks, and a requirement for treatment with at least intermittent diuretic, NYHA functional Classes II–IV, LVEF >40%, evidence of structural heart disease (either left-atrial enlargement or left-ventricular hypertrophy), and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥300 pg/mL (≥600 pg/mL if atrial fibrillation/flutter on the electrocardiogram at enrolment). Key exclusion criteria Type 1 diabetes mellitus (T1D) 3. eGFR <25ml/min/1.73m², unstable CVD, A life expectancy of less than 2 years due to any non-cardiovascular condition Randomisation was stratified for DM+ or DM-
Intervention/comparison	dapagliflozin 10 mg vs placebo

	in addition to standard of care therapy
Outcomes	**Primary outcomes:** composite of worsening heart failure, which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure, or cardiovascular death. **Secondary end points** total number of worsening heart failure events and cardiovascular deaths, the change from baseline in the total symptom score on the Kansas City Cardiomyopathy Questionnaire at month 8 Cardiovascular death Death from any cause
Methodology	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -dapagliflozin arm: vital status unknown at the end of the trial in 2/3131 patients. -Placebo arm: vital status unknown at the end of the trial in 2/3132 patients. ITT: yes (all randomised patients are included in the efficacy analysis according to randomised treatment assignment) Sponsor:

	AstraZeneca

12.1.1.3.1 DM

Inzucchi 2022(22) SUBGROUP of DELIVER	SUBGROUP DIABETES vs NO DIABETES Subgroup variables for the primary efficacy endpoint include demography, baseline disease characteristics, baseline concomitant medications and others. The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively. <u>Baseline characteristics</u> History of type 2 diabetes: 2806/6263 (44.8%) dapagliflozin: 1401/3131 (44.7%) placebo: 1405/3132 (44.9%) Inzucchi 2022: <u>Prespecification</u> Yes, for primary outcome

For purposes of this analysis, the trial population was divided as prespecified in the trial's statistical analysis plan (appendix 1 pp 225–293)13 into the following categories based on glycaemic status at baseline, derived from criteria of the American Diabetes Association: patients with **normoglycaemia** (no history of diabetes and baseline HbA1c <5·7% [39 mmol/mol]); those with **prediabetes** (no history of diabetes and baseline HbA1c 5·7to <6·5% [39 mmol/mol to <48 mmol/mol]; and those with **type 2 diabetes** (history of or prevalent use of a glucose-lowering agent [unless specifically prescribed for an indication other than diabetes]) or baseline HbA1c ≥6·5% [48 mmol/mol]).

the main analysis reported in this article was prespecified.

Baseline characteristics

Type 2 diabetes: 3150 (50.3%) (2806 [44·8%] based on history, 26 [0·4%] based on medication use, and 318 [5·1%] newly identified by baseline HbA1c level)

Prediabetes: 1934 (30.9%)

Normoglycemia: 1175 (18.8%)

Solomon 2022(21) Inzucchi 2022(22);	
Outcomes	
Efficacy	

Composite of worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	Overall HR 0.82 (0.73-0.92) p<0.001 **SS** SUBGROUP Diabetes HR 0.83 (0.70 to 0.97) No diabetes HR 0.81 (0.68 to 0.96) **Interaction p value**: NR Effect of dapagliflozin on primary outcome described as being consistent across all prespecified subgroups SUBGROUP Normoglycemia HR 0·77 (0·57–1·04) Prediabetes HR 0·87 (0·69–1·08) Type 2 diabetes HR 0·81 (0·69–0·95) **Interaction p value**: 0.82	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

CV death	Overall HR 0.88 (0.74 to 1.05) P NA SUBGROUP Normoglycemia HR 0·82 (0·54–1·23) Prediabetes HR 1·02 (0·72–1·43) Type 2 diabetes HR 0·85 (0·67–1·08) **Interaction p value**: 0.63	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Heart failure event (hospitalization or urgent visit)	Overall HR 0.79 (0.73-0.91) P NA SUBGROUP Normoglycemia HR 0·76 (0·53–1·10) Prediabetes HR 0·73 (0·56–0·95) Type 2 diabetes HR 0·83 (0·69–0·99) **Interaction p value**: 0.74	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Heart failure hospitalization	Overall HR 0.77 (0.67-0.89) P NA SUBGROUP Normoglycemia HR 0·69 (0·47–1·00) Prediabetes HR 0·74 (0·56–0·98) Type 2 diabetes HR 0·81 (0·67–0·98) **Interaction p value**: 0.72	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Urgent heart failure visit	Overall HR 0.76 (0.55 to 1.07) P NA SUBGROUP Normoglycemia HR 1·73 (0·51–5·91) Prediabetes HR 0·59 (0·31–1·11) Type 2 diabetes HR 0·78 (0·51–1·19) **Interaction p value**: 0.38	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Composite of cardiovascular death and all heart failure events (including recurrent)	Overall RR 0.77 (0.67 to 0.89) P <0.001 SS SUBGROUP Normoglycemia RR 0·71 (0·50–1·01) Prediabetes RR 0·70 (0·54–0·92) Type 2 diabetes RR 0·82 (0·68–0·99) **Interaction p value**: 0.58	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Death from any cause	Overall HR 0.94 (0.83 to 1.07) P NA SUBGROUP Normoglycemia HR 0.80 (0·60–1·07) Prediabetes HR 1·14 (0·90–1·44) Type 2 diabetes HR 0·91 (0·77–1·07) **Interaction p value**: 0.14	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Safety		
No analysis of modification of dapagliflozin effect by diabetes status		

12.1.1.3.2 CKD

Mc Causland 2023(38)	SUBGROUP eGFR ≥60 mL/min/1.73 m² vs eGFR 45 to <60 mL/min/1.73 m² vs eGFR <45 mL/min/1.73 m²
SUBGROUP of DELIVER	Prespecified analyses included assessment of the influence of baseline kidney function (eGFR ≥60 mL/min/1.73 m2, eGFR 45 to <60 mL/min/1.73 m2, eGFR <45 mL/min/1.73 m2, and eGFR as a continuous variable) on the effect of dapagliflozin vs placebo **on the primary outcome.**

Baseline characteristics

eGFR ≥60 mL/min/1.73 m2: 3192/6262 (51%)
eGFR 45 to <60 mL/min/1.73 m2: 1657/6262 (26%)
eGFR <45 mL/min/1.73 m2: 1413/6262 (23%)

Mc Causland 2023		
Outcomes		
Efficacy		
worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	Overall HR 0.82 (0.73-0.92) p<0.001 **SS** SUBGROUP CKD (eGFR<60mL/min/1.73m²) HR 0.81 (0.69 to 0.94) No CKD (eGFR≥60mL/min/1.73m²) HR 0.84 (0.70 to 1.00) **Interaction p value**: NR	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

	Effect of dapagliflozin on primary outcome described as being consistent across all prespecified subgroups SUBGROUP <u>eGFR ≥60 mL/min/1.73 m2</u> HR 0.84 (0.70-1.00) <u>eGFR 45 to <60 mL/min/1.73 m2</u> HR 0.68 (0.54-0.87) <u>eGFR <45 mL/min/1.73 m2</u> HR 0.93 (0.76-1.14) **Interaction p value**: 0.16 when using eGFR as a continuous variable, there was no evidence for differential treatment effects according to baseline kidney function (CV death: P for interaction = .99; heart failure events: P for interaction = .30; heart failure hospitalization: P for interaction = .52).	

CV death	Overall HR 0.88 (0.74 to 1.05) P NA SUBGROUP eGFR ≥60 mL/min/1.73 m2 HR 0.92 (0.70-1.21) eGFR 45 to <60 mL/min/1.73 m2 HR 0.87 (0.61-1.23) eGFR <45 mL/min/1.73 m2 HR 0.87 (0.64-1.20) **Interaction p value**: 0.96	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Heart failure event (hospitalization or urgent visit)	Overall HR 0.79 (0.69-0.91) P NA SUBGROUP eGFR ≥60 mL/min/1.73 m2 HR 0.79 (0.64-0.98) eGFR 45 to <60 mL/min/1.73 m2 HR 0.59 (0.44-0.79) eGFR <45 mL/min/1.73 m2 HR 0.97 (0.77-1.22) **Interaction p value**: 0.04	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** YES

Heart failure hospitalization	Overall HR 0.77 (0.67-0.89) P NA SUBGROUP eGFR ≥60 mL/min/1.73 m2 HR 0.81 (0.65-1.02) eGFR 45 to <60 mL/min/1.73 m2 HR 0.56 (0.41-0.76) eGFR <45 mL/min/1.73 m2 HR 0.90 (0.71-1.15) **Interaction p value**: 0.05	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Worsening kidney function Mean decline in eGFR	Overall MD: 1.4 (95% CI, 1.0-1.8) mL/min/1.73 m2per year P<0.001 SUBGROUP eGFR ≥60 mL/min/1.73 m2 MD 1.7 (1.1, 2.3) eGFR 45 to <60 mL/min/1.73 m2 MD 1.1 (0.4, 1.9) eGFR <45 mL/min/1.73 m2 MD 0.9 (0.1,1.7) **Interaction p value**: 0.29	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Kidney composite end point (≥50% decline in eGFR, end-stage kidney disease or death from kidney causes) (**post hoc definition)**	Overall HR 1.08 (0.79-1.49) SUBGROUP eGFR ≥60 mL/min/1.73 m2 HR 1.06 (0.66-1.70) eGFR 45 to <60 mL/min/1.73 m2 HR 0.80 (0.41-1.57) eGFR <45 mL/min/1.73 m2 HR 1.46 (0.83-2.56) **Interaction p value**: 0.34	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		

No analysis of modification of dapagliflozin effect by kidney function	

12.1.1.3.3 COPD

Butt 2023(52) SUBGROUP Of DELIVER	SUBGROUP history of COPD vs no history of COPD at baseline COPD status was **not** included as one of the 14 prespecified subgroups. Data on medical history, including COPD, were investigator-reported and retrieved from the trial electronic case report forms. <u>Baseline characteristics</u> History of COPD 694/6269 (11.1%)

Outcomes	
Efficacy	

Composite of worsening HF episode (hospitalization or the equivalent, i.e. an urgent HF visit) or cardiovascular death **(primary outcome)**	Overall HR 0.82 (0.73-0.92) p<0.001 **SS** SUBGROUP No COPD HR 0.82 (0.72–0.93) COPD HR 0.82 (0.62–1.10) **Interaction p value**: 0.98	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Composite of cardiovascular death and all heart failure events (including recurrent)	Overall RR 0.77 (0.67 to 0.89) P <0.001 SS SUBGROUP No COPD RR 0.82 (0.72–0.93) COPD RR 0.82 (0.62–1.10) **Interaction p value**: 0.70	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Heart failure hospitalization	Overall RR 0.77 (0.67-0.89) P NA SUBGROUP No COPD RR 0.71 (0.59–0.86) COPD RR 0.73 (0.47–1.13) **Interaction p value**: 0.90	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Cardiovascular hospitalizations	Overall group Not reported SUBGROUP No COPD RR 0.85 (0.73–0.97) COPD RR 0.78 (0.56–1.10) **Interaction p value**: 0.69	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

All-cause hospitalizations	Overall group Not reported SUBGROUP No COPD RR 0.89 (0.81–0.98) COPD RR 0.89 (0.71–1.13) **Interaction p value**: 0.96	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
CV death	Overall HR 0.88 (0.74 to 1.05) P NA SUBGROUP No COPD HR 0.85 (0.70–1.03) COPD HR 1.06 (0.70–1.61) **Interaction p value**: 0.35	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Death from any cause	Overall HR 0.94 (0.83 to 1.07) P NA SUBGROUP No COPD HR 0.93 (0.81–1.06) COPD HR 1.02 (0.74–1.41) **Interaction p value**: 0.59	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause deaths and all-cause hospitalizations	Overall group Not reported SUBGROUP No COPD RR 0.90 (0.82–0.98) COPD RR 0.91 (0.73–1.14) **Interaction p value**: 0.83	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

KCCQ-TSS (change from baseline to 8 months)	Overall 1.11 (1.03–1.21) P 0.009 SUBGROUP No COPD 2.3 (1.3–3.4) COPD 2.6 (−0.6 to 5.8) **Interaction p value**: 0.78	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
	No significant p-value for interaction for • Discontinuation of study drug due to adverse event • Volume depletion • Renal adverse event • Amputation • Major hypoglycemia • Diabetic ketoacidosis	

12.1.1.3.4 BMI

Solomon 2022(21); Adamson 2022(49): DELIVER SUBGROUP Of DELIVER	• SUBGROUP BMI>30 vs BMI<30 • SUBGROUP 5 BMI categories: BMI 18.5–24.9 kg/m² ; BMI 25.0–29.9 kg/m²; BMI 30.0–34.9 kg/m²; BMI 35.0–39.9 kg/m²; BMI ≥40 kg/m² <u>Prespecified:</u> • Analysis by **BMI category <30 kg/m² compared with ≥30 kg/m²** was a **pre-specified** subgroup analysis in DELIVER for the **primary endpoint** and for **CV death** and the **HF event** (hospitalisation for HF and urgent HF visit) component of the primary composite endpoint. • Analysis by **5 BMI categories was not prespecified** Other important methodological remarks: • The p-values for the subgroup analyses and interaction were not be adjusted for multiple comparisons <u>Baseline characteristics</u> 6263 randomized; 6257 with recorded BMI measurement at baseline BMI>30: 2787/6257 (45%) BMI 18.5–24.9 kg/m²: 1343/6257 (21%) BMI 25.0–29.9 kg/m²: 2073/6257 (33%) BMI 30.0–34.9 kg/m²: 1574/6257 (25%) BMI 35.0–39.9 kg/m²: 798/6257 (13%) BMI ≥40 kg/m²: 415/6257 (7%)

Outcomes	

Efficacy		
composite outcome of worsening heart failure (hospitalization or an urgent visit) **or death from cardiovascular causes** **(primary outcome)**	Overall 512/3131 vs 610/3132 HR 0.82 (0.73-0.92) p<0.001 **SS** BMI <30 275/1734 vs 302/1736 HR 0.89 (0.75-1.04) BMI ≥30 236/1395 vs 308/1392 HR 0.74 (0.63-0.88) **Interaction test**: not done	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
	BMI 18.5–24.9 kg/m² HR 0.89 (0.69–1.15) BMI 25.0–29.9 kg/m² HR 0.87 (0.70–1.08) BMI 30.0–34.9 kg/m² HR 0.74 (0.58–0.93) BMI 35.0–39.9 kg/m² HR 0.78 (0.57–1.08) BMI ≥40 kg/m² HR 0.72 (0.47–1.08) **Interaction test**: p=0.82	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Worsening heart failure (hospitalization for heart failure or an urgent visit) events and cardiovascular deaths	Overall 815/3131 vs 1057/3132 Rate ratio 0.77 (0.67-0.89) p<0.001 **SS** BMI 18.5–24.9 kg/m² Rate ratio 0.93 (0.69–1.25) BMI 25.0–29.9 kg/m² Rate ratio 0.78 (0.60–1.01) BMI 30.0–34.9 kg/m² Rate ratio 0.62 (0.47–0.82) BMI 35.0–39.9 kg/m² Rate ratio 0.80 (0.55–1.18) BMI ≥40 kg/m² Rate ratio 0.71 (0.45–1.12) **Interaction test**: p=0.44	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Change in KCCQ-TSS at 8 months Placebo-corrected change at 8 months (Mixed-effect models for repeated measurements adjusted for baseline value, visit (Months 1, 4, and 8), randomized treatment, and interaction of treatment and visit.)	Overall Win ratio 1.11 (1.03-1.21) p=0.009 **SS** mean placebo-corrected difference between baseline and month 8 among survivors, 2.4 points; 95% CI, 1.5 to 3.4) BMI 18.5–24.9 kg/m² 0.9 (−1.1, 2.8) BMI 25.0–29.9 kg/m² 2.5 (0.8, 4.1) BMI 30.0–34.9 kg/m² 1.9 (−0.1, 3.8) BMI 35.0–39.9 kg/m² 2.7 (−0.5, 5.8) BMI ≥40 kg/m² 8.6 (4.0, 13.2) **Interaction test**: **p=0.03**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** YES
Worsening heart failure event	Overall 368/3131 vs 455/3132 HR 0.79 (0.69–0.91) Interaction test: p=0.66	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Cardiovascular death	Overall 231/3131 vs 261/3132 HR 0.88 (0.74–1.05) Interaction test: p=0.89	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause death	Overall 497/3131 vs 526/3132 HR 0.94 (0.83–1.07) Interaction test: p=0.82	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
AE leading to discontinuation of randomized treatment	Interaction test: p=0.79	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Amputation	Interaction test: p=0.84	
Definite or probable DKA	Interaction test: p= NA	
Major hypoglycaemic event	Interaction test: p=0.92	
Volume depletion SAE/DAE	Interaction test: p=0.64	
Renal SAE/DAE	Interaction test: p=0.58	

12.1.2 Empagliflozin vs placebo

12.1.2.1 EMPEROR-REDUCED (HFrEF)

Ref Packer 2020(23)	**EMPEROR-R** trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction)
Study details	Design: RCT ; Double-blind, parallel group Duration of follow-up: 16 months
n/population	n= 3730 randomized Mean age: -Empagliflozin: 67.2 yr -placebo: 66.5 yr Inclusion criteria patients ≥18 years who had chronic HF (NYHA II, III, or IV) with a **LVEF ≤40%** Exclusion criteria symptomatic hypotension, systolic blood pressure of <100 mmHg or ≥180 mmHg, or an estimated glomerular filtration rate **(eGFR) <20 mL/min/1.73 m²**

	Randomization was stratified according to geographical region (North America, Latin America, Europe, Asia, or other), **diabetes status at screening,** and **eGFR at screening** (<60 or ≥60 ml/min/1.73 m2)
Intervention/comparison	Empagliflozin 10 mg vs placebo Patients were receiving all appropriate treatments for heart failure as available and tolerated.
Outcomes	**Primary outcome:** composite of adjudicated cardiovascular death or hospitalization for heart failure, analyzed as the time to the first event. **Secondary outcomes** 1. First and recurrent HHF 2. Renal slope (eGFR mean slope change/year) **Exploratory outcomes** including a composite renal outcome, total hospitalizations for any reason, and quality of life
Methodological	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -empagliflozin arm (n=1863): there was incomplete follow-up for the primary endpoint in 22 patients. -Placebo arm (n=1867): there was incomplete follow-up for the primary endpoint in 20 patients. ITT: Yes for primary analysis (all randomized patients analysed)

	Sponsor: Boehringer Ingelheim and Eli Lilly

12.1.2.1.1 DM

SUBGROUP Anker 2021b(24) Of EMPEROR-Reduced trial	SUBGROUP DIABETES vs NO DIABETES <u>Prespecified ?</u> Prespecified subgroup analyses for the primary outcome included baseline **diabetes** status (yes/no); baseline **BMI** (≥ or <30); baseline **eGFR** ((≥ or <60 ml/min/1.73m²; five eGFR categories) From protocol: Subgroups planned for the primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent), renal slope. <u>Baseline characteristics</u> Diabetes 1856 (50%) No diabetes: 1874 (50%); Prediabetes (34%) Normoglycemic (16%)

Outcomes		
Efficacy		
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall HR 0.75 (0.65-0.86) p<0.001 **SS** SUBGROUP Diabetes HR 0.72 (0.60-0.87) No diabetes HR 0.78 (0.64-0.97) **Interaction p value**: 0.57	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
First and recurrent HHF	Overall: HR 0.70 (0.58, 0.85) SS SUBGROUP Diabetes HR 0.65 (0.50, 0.85) No diabetes HR 0.76 (0.57, 1.01) **Interaction p value**: 0.44	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

Renal slope (eGFR mean slope change/year)	Overall: Difference 1.73 (1.10, 2.37) SS SUBGROUP Diabetes HR 2.21 (1.31, 3.10) No diabetes HR 1.27 (0.38, 2.16) **Interaction p value**: 0.15	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
Composite renal endpoint (the need for chronic dialysis or renal transplant or a ≥40% sustained reduction in eGFR or a sustained eGFR <15ml/min/1.73 m2 (if baseline eGFR was ≥30 ml/min/1.73 m2) or <10 ml/min/1.73 m2 (if baseline eGFR was <30 ml/min/1.73 m2)	Overall: HR 0.50 (0.32-0.77) SUBGROUP Diabetes HR 0.53 (0.31, 0.90) No diabetes HR 0.42 (0.19, 0.97) **Interaction p value**: 0.65	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
First HHF	Overall: HR 0.69 (0.59, 0.81) SUBGROUP Diabetes HR 0.67 (0.54, 0.83)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES

	No diabetes HR 0.72 (0.56, 0.93) **Interaction p value**: 0.66	**Was the test of interaction significant (interaction P <0.05)?** NO
Time to CV death	Overall: HR 0.92 (0.75, 1.12) SUBGROUP Diabetes HR 0.92 (0.71, 1.20) No diabetes HR 0.92 (0.68, 1.24) **Interaction p value**: 0.98	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
Changes in KCCQ clinical summary score at week 52	Overall: Difference 1.75 (0.5, 3.0) SUBGROUP Diabetes HR 2.41 (0.64, 4.17) No diabetes HR 1.10 (−0.64, 2.85) **Interaction p value**: 0.30	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Safety	
Other than genital tract infections, there were no meaningful increases in the empagliflozin group and the pattern of between-group differences was not influenced by the presence or absence of diabetes. No statistical significance testing. No test of interaction.	

12.1.2.1.2 CKD

Zannad 2021(39) SUBGROUP Of EMPEROR-Reduced trial	SUBGROUP CKD vs NO CKD <u>Prespecified ?</u> Prespecified subgroup analyses for the primary outcome included baseline **diabetes** status (yes/no); baseline **BMI** (≥ or <30); baseline **eGFR** ((≥ or <60 ml/min/1.73m²; five eGFR categories (<30, 30–44, 45–59, 60–89, and ≥90 ml/min/1.73 m2) From protocol: Subgroups planned for the primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent), renal slope. <u>Baseline characteristics</u> CKD 1978 (53%)

Outcomes		
Efficacy		
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall HR 0.75 (0.65-0.86) p<0.001 **SS** SUBGROUP CKD HR 0.78 (0.65-0.93) No CKD HR 0.72 (0.58-0.90) **Interaction p value**: 0.63 --- SUBGROUP eGFR≥90 HR 0.51 (0.33 to 0.80) eGFR 60 to <90 HR 0.73 (0.58 to 0.92) eGFR 45 to <60	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

	HR 0.76 (0.57 to 1.02) <u>eGFR 30 to <45</u> HR 0.92 (0.69 to 1.23) <u>eGFR <30</u> HR 0.68 (0.42 to 1.09) **Interaction p value**: 0.12	
First and recurrent HHF	Overall: HR 0.70 (0.58, 0.85) SS SUBGROUP <u>CKD</u> HR 0.73 (0.57-0.94) <u>No CKD</u> HR 0.69 (0.51-0.93) **Interaction p value**: 0.78 --- SUBGROUP <u>eGFR≥90</u>	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

	HR 0.35 (0.19 to 0.63) eGFR 60 to <90 HR 0.70 (0.51 to 0.96) eGFR 45 to <60 HR 0.71 (0.48 to 1.06) eGFR 30 to <45 HR 0.99 (0.65 to 1.50) eGFR <30 HR 0.59 (0.28 to 1.23) **Interaction p value**: 0.06	
Renal slope (eGFR mean slope change/year)	Overall: Difference 1.73 (1.10, 2.37) SS SUBGROUP CKD 1.11(0.23 to 1.98) No CKD 2.41 (1.49 to 3.32) **Interaction p value**: 0.045 --- SUBGROUP eGFR≥90 Difference 1.96 (0.16 to 3.76)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** YES

	eGFR 60 to <90 Difference 2.49 (1.49 to 3.49) eGFR 45 to <60 Difference 1.62 (0.35 to 2.89) eGFR 30 to <45 Difference 0.43 (-1.06 to 1.93) eGFR <30 Difference 0.63 (-2.31 to 3.56) **Interaction p value**: 0.033	
Composite renal endpoint (the need for chronic dialysis or renal transplant or a ≥40% sustained reduction in eGFR or a sustained eGFR <15ml/min/1.73 m2 (if baseline eGFR was ≥30 ml/min/1.73 m2) or <10 ml/min/1.73 m2 (if baseline eGFR was <30 ml/min/1.73 m2)	Overall: HR 0.50 (0.32-0.77) SS SUBGROUP CKD HR 0.53 (0.31-0.91) No CKD HR 0.46 (0.22-0.99) ---- **Interaction p value**: 0.78 SUBGROUP eGFR≥90 not calculated as <14 events in subgroup eGFR 60 to <90 HR 0.52 (0.26 to 1.05) eGFR 45 to <60	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

	HR 0.88 (0.37 to 2.11) eGFR 30 to <45 HR 0.33 (0.12 to 0.90) eGFR <30 not calculated as <14 events in subgroup **Interaction p value**: 0.74	
Safety		
no excess adverse events in patients receiving empagliflozin, as compared to patients receiving placebo, across all categories of kidney function. No statistical significance testing reported No test of interaction reported See table		

12.1.2.1.3 BMI

Anker 2023(50): EMPEROR-R
 	
SUBGROUP
	• SUBGROUP BMI>30 vs BMI<30
	• SUBGROUP 5 BMI categories: (*The authors chose BMI 20 kg/m² as the lower cut-off and 35 kg/m² as the higher cut-off due to low sample size below BMI 20 kg/m² and above 35 kg/m².)*
	  ○ BMI <20 kg/m^2
	  ○ BMI 20 to <25 kg/m^2
	  ○ BMI 25 to <30 kg/m^2

Of EMPEROR-REDUCED	○ BMI 30 to <35 kg/m2 ○ BMI ≥35 kg/m^2 Prespecified: • Analysis by **BMI category <30 kg/m² compared with ≥30 kg/m²** was a **pre-specified** subgroup analysis in EMPEROR-Reduced for multiple efficacy endpoints (**primary endpoint, time to cardiovascular (CV) death, time to first HHF, HHF (first and recurrent), renal slope)** • Analysis by **5 BMI categories was not prespecified** Other important methodological remarks: • The p-values for the subgroup analyses and interaction were not be adjusted for multiple comparisons • The slope of the estimated GFR was analyzed on the basis of on-treatment data with a random coefficient model that included age and baseline estimated GFR as linear covariates and sex, region, baseline left ventricular ejection fraction, baseline diabetes status, baseline estimated GFR according to time, and treatment according to time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients. Baseline characteristics BMI>30: 1506/3730 (40%) BMI <20 kg/m²: 180/3730 (5%) BMI 20 to <25 kg/m²: 1038/3730 (28%) BMI 25 to <30 kg/m²: 1345/3730 (36%) BMI 30 to <35 kg/m²: 774/3730 (21%) o BMI ≥35 kg/m²: 393/3730 (11%)

Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall 361/1863 vs 462/1867 HR 0.75 (0.65-0.86) p<0.001 **SS** BMI <30 226/1263 vs 322/1300 HR 0.70 (0.59-0.83) BMI ≥30 135/600 vs 140/567 HR 0.85 (0.67-1.08) **Interaction test**: not done	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
	BMI <20 kg/m2 24/91 vs 24/89 HR 0.85 (0.48, 1.50) BMI 20 to <25 kg/m2 95/508 vs 139/530 HR 0.66 (0.51, 0.86) BMI 25 to <30 kg/m2 107/664 vs 159/681 HR 0.69 (0.54, 0.89) BMI 30 to <35 kg/m2 92/406 vs 88/368 HR 0.88 (0.65, 1.18) BMI ≥35 kg/m2 43/194 vs 52/199 HR 0.82 (0.55, 1.23)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	Interaction test: p=0.32	
Total HHF	Overall: HR 0.70 (0.58, 0.85) p<0.001 **SS** <u>BMI <20 kg/m2</u> HR 0.81 (0.34, 1.91) <u>BMI 20 to <25 kg/m2</u> HR 0.58 (0.41, 0.84) <u>BMI 25 to <30 kg/m2</u> HR 0.71 (0.51, 0.98) <u>BMI 30 to <35 kg/m2</u> HR 0.68 (0.45, 1.02) <u>BMI ≥35 kg/m2</u> HR 0.94 (0.54, 1.64) . **Interaction test**: p= 0.31	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Renal slope (eGFR mean slope change/year)	Overall: Difference 1.73 (1.10, 2.37) p<0.001 **SS** BMI <20 kg/m2 Difference 3.25 (0.36 to 6.12) BMI 20 to <25 kg/m2 Difference 2.02 (0.86 to 3.19) BMI 25 to <30 kg/m2 Difference 0.96 (-0.10 to 2.02) BMI 30 to <35 kg/m2 Difference 2.63 (1.22 to 4.04) BMI ≥35 kg/m2 Difference 1.36 (-0.65 to 3.36) **Interaction test**: p= 0.67	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
First HHF	Overall 246/1863 vs 342/1867 HR 0.69 (0.59, 0.81) BMI<20 13/91 vs 17/89 HR 0.66 (0.32, 1.36) BMI 20 – BMI <25 52/508 vs 103/530 HR 0.58 (0.42, 0.79) BMI 25 – BMI <30 68/664 vs 115/681 HR 0.61 (0.45-0.82) BMI 30 – BMI <35 66/406 vs 70/368 HR 0.81 (0.57, 1.13)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** YES

	BMI≥35 37/194 vs 37/199 HR 1.00 (0.63, 1.57) **Interaction test: p= 0.04**	
CV death	Overall: HR 0.92 (0.75, 1.12) BMI <20 kg/m2 HR 1.31 (0.53, 2.43) BMI 20 to <25 kg/m2 HR 0.87 (0.60, 1.25) BMI 25 to <30 kg/m2 HR 0.89 (0.63, 1.24) BMI 30 to <35 kg/m2 HR 1.16 (0.73, 1.86 BMI ≥35 kg/m2 HR 0.72 (0.37, 1.39) **Interaction test**: p= 0.86	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause mortality	Overall: HR 0.92 (0.77, 1.10) BMI <20 kg/m2 HR 0.90 (0.48, 1.67) BMI 20 to <25 kg/m2 HR 0.93 (0.67, 1.28) BMI 25 to <30 kg/m2 HR 0.88 (0.66, 1.18) BMI 30 to <35 kg/m2 HR 1.13 (0.75, 1.70 BMI ≥35 kg/m2 HR 0.79 (0.46, 1.37)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	Interaction test: p= 0.99	
Composite renal endpoint (the need for chronic dialysis or renal transplant or a ≥40% sustained reduction in eGFR or a sustained eGFR <15ml/min/1.73 m2 (if baseline eGFR was ≥30 ml/min/1.73 m2) or <10 ml/min/1.73 m2 (if baseline eGFR was <30 ml/min/1.73 m2)	Overall: HR 0.50 (0.32-0.77) Results per BMI category: NR **Interaction test**: p= 0.76	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Changes in KCCQ clinical summary score at week 52	Overall: Difference 1.61 (0.39, 2.84) <u>BMI <20 kg/m2</u> Difference -1.03 (-9.70, 1.64) <u>BMI 20 to <25 kg/m2</u> Difference 2.81 (0.51, 5.10) <u>BMI 25 to <30 kg/m2</u> Difference 1.96 (-0.09, 4.02) <u>BMI 30 to <35 kg/m2</u> Difference 1.10 (-1.60, 3.80) <u>BMI ≥35 kg/m2</u> Difference 1.34 (-2.47, 5.15) **Interaction test**: p > 0.99	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
Patients with any AE	No analysis of modification of empagliflozin effect by BMI category	
Patients with AEs leading to drug discontinuation		
Patients with serious AEs		

Symptomatic hypotension		
Acute renal failure		
Confirmed hypoglycemia		
Genital infection		

12.1.2.2 EMPEROR-Preserved (HFpEF)

Anker 2021a(26)	**EMPEROR-PRESERVED trial** (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction)
Study details	Design: RCT ; Double-blind, parallel group Duration of follow-up: Median 26.2 months
n/population	n= 5988 Mean age: -Empagliflozin (n=2997): 71.8 ±9.3 yr -Placebo (n=2991): 71.9 ±9.6 yr Inclusion criteria • HFpEF patients ≥18 years; • NYHA II-IV for at least 3 months and a **LVEF of >40%** with no prior measurement of ≤40%; • elevated N-terminal pro-B-type natriuretic peptide levels (>900 or >300 pg/ml in patients with or without atrial fibrillation, respectively); • a documented hospitalization for HF or evidence of structural heart disease (increased left ventricular mass or left atrial size) within the last 12months.; • BMI <45 kg/m2 at Screening Key exclusion criteria

	• Any disorder that could change their clinical course, independent of heart failure, or if they had any condition that might jeopardize patient safety or limit their participation in the trial • Chronic pulmonary disease requiring home oxygen, oral corticosteroid therapy or hospitalisation for exacerbation within 12 months; significant chronic pulmonary disease; or primary pulmonary arterial hypertension • than three times the upper limit of normal at screening • Impaired renal function, defined as eGFR < 20 mL/min/1.73 m2 (CKD-EPI) or requiring dialysis at the time of screening Randomization was stratified by geographic region, **diabetes status**, estimated glomerular filtration rate (**eGFR**) of less than 60 ml per minute per 1.73 m^2 of body-surface area or 60 ml or more per minute per 1.73 m^2 , and left ventricular ejection fraction of less than 50% or 50% or more, all measured at screening
Intervention/comparison	Empagliflozin 10 mg vs placebo in addition to usual therapy
Outcomes	**Primary outcome:** 1. composite of adjudicated cardiovascular death or hospitalization for heart failure (analyzed as the time to the first event) The individual components of the primary endpoints, i.e., time to first hospitalization for heart failure and time to cardiovascular death **Key secondary end points** 1. the occurrence of all adjudicated hospitalizations for heart failure, including first and recurrent events. 2. the rate of decline (slope) in the eGFR during double-blind treatment. **Additional secondary end points (not included in testing hierarchy)** 1. Composite renal endpoint 2. . Change from baseline in clinical summary score (KCCQ) at week 52 3. Total (first and recurrent) hospitalizations for any reason 4. Time to all-cause mortality

Methodology	5. Time to onset of diabetes RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -empagliflozin arm (n=2997): 1 patient did not start treatment and there was incomplete follow-up for the primary endpoint in 84 patients. -Placebo arm (n=2991): 2 patients did not start treatment and there was incomplete follow-up for the primary endpoint in 88 patients. ITT: yes (all randomized patients included in primary analysis) Sponsor: Boehringer Ingelheim and Eli Lilly

12.1.2.2.1 DM

Filippatos 2022(27)	SUBGROUP DIABETES vs NO DIABETES

SUBGROUP of EMPEROR-PRESERVED	Prespecified? Yes, 15 prespecified subgroups (for analysis of the **primary endpoint**) included diabetes at baseline (yes/no); BMI at baseline (≥30/<30); eGFR at baseline (≥ or < 60 ml/min/1.73m² No for the other endpoints. Other remarks on methods -For all hazard ratios or treatment differences not included in the testing hierarchy, no adjustment has been made for multiple comparisons, so the intervals should not be used to infer definitive treatment effects. Baseline characteristics Diabetes Mellitus 2938 (49%) -placebo: 48.9% -empagliflozin: 49.2%

Outcomes	
Efficacy	

Composite outcome cardiovascular mortality or HF hospitalization **(primary outcome)**	Overall HR 0.79 (0.69-0.90) <0.001 **SS** SUBGROUP No diabetes HR 0.78 (0.64, 0.95) Diabetes HR 0.79 (0.67, 0.94) **Interaction p value 0.92**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
First and recurrent HFF	Overall 0.73 (0.61, 0.88) <0.001 SS SUBGROUP No diabetes HR 0.74 (0.56, 0.97) Diabetes HR 0.73 (0.57, 0.94) **Interaction p value 0.97** **NS**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Time to first HHF	Overall	**Was the subgroup variable a baseline characteristic?**

	HR 0.71 (0.60, 0.83) SUBGROUP No diabetes HR 0.74 (0.57, 0.96) Diabetes HR 0.69 (0.56, 0.85) **Interaction p value 0.66** **NS**	YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Time to CV death	Overall HR 0.91 (0.76, 1.09) SUBGROUP No diabetes HR 0.82 (0.63, 1.07) Diabetes HR 0.99 (0.77, 1.27) **Interaction p value 0.32** **NS**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Time to all-cause mortality	Overall HR 1.00 (0.87, 1.15)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?**

	SUBGROUP No diabetes HR 0.94 (0.77, 1.15) Diabetes HR 1.05 (0.88, 1.26) **Interaction p value 0.43** **NS**	NO **Was the test of interaction significant (interaction P <0.05)?** NO
Composite renal end point* *Time to first occurrence of (1) chronic dialysis; (2) renal transplantation; (3) sustained reduction of ≥40% in estimated glomerular filtration rate (eGFR); or (4) sustained eGFR <15 mL/min/1.73m2 for patients with baseline eGFR ≥30 mL/min/1.73m2 or <10 mL/min/1.73m2 for patients with baseline eGFR <30 mL/min/1.73m2.	Overall HR 0.95 (0.73,1.24) SUBGROUP No diabetes HR 0.87 (0.54, 1.38) Diabetes HR 1.00 (0.72, 1.38) **Interaction p value 0.62** **NS**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Siddiqi 2023(28) SUBGROUP of EMPEROR-PRESERVED	SUBGROUP DIABETES vs NO DIABETES <u>Prespecified?</u> No, not for this endpoint. <u>Other remarks on methods</u> -For all hazard ratios or treatment differences not included in the testing hierarchy, no adjustment has been made for multiple comparisons, so the intervals should not be used to infer definitive treatment effects. <u>Baseline characteristics</u> Diabetes Mellitus 2938 (49%) -placebo: 48.9% -empagliflozin: 49.2%

Outcomes
KCCQ CSS at week 52

Kansas City Cardiomyopathy Questionnaire (KCCQ) changes in clinical summary score at 52 weeks	<u>Overall</u> 4.51±0.31 vs 3.18±0.31 Difference 1.32 (0.45-2.19) SUBGROUP <u>No diabetes</u> Difference 1.21 (0.02, 2.41) <u>Diabetes</u> Difference 1.79 (0.56, 3.03) Interaction p value: 0.511	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

12.1.2.2.2 CKD

Sharma 2023(40) SUBGROUP of EMPEROR-PRESERVED	SUBGROUP CKD vs NO CKD <u>Prespecified?</u> Yes, 15 prespecified subgroups (for analysis of the **primary endpoint**) included diabetes at baseline (yes/no); BMI at baseline (≥30/<30); eGFR at baseline (≥ or < 60 ml/min/1.73m²) No for the other endpoints. <u>Other remarks on methods</u> -For all hazard ratios or treatment differences not included in the testing hierarchy, no adjustment has been made for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

Baseline characteristics
eGFR < 60 ml/min: 3198/5988 (53.4%)
-placebo: 50.2%
-empagliflozin: 49.6%

Outcomes		
Efficacy		
Composite outcome cardiovascular mortality or HF hospitalization **(primary outcome)**	Overall HR 0.79 (0.69-0.90) **SS** SUBGROUP No CKD HR 0.75 (0.60, 0.95) CKD HR 0.80 (0.69, 0.94) **Interaction p value 0.6682**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
First and recurrent HFF	Overall HR 0.73 (0.61, 0.88) SUBGROUP No CKD HR 0.89 (0.66, 1.21)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO

	CKD HR 0.68 (0.54, 0.86) **Interaction p value 0.1677**	**Was the test of interaction significant (interaction P <0.05)?** NO
Time to first HHF	Overall HR 0.71 (0.60, 0.83) SUBGROUP No CKD HR 0.73 (0.54, 1.00) CKD HR 0.70 (0.58, 0.84) **Interaction p value 0.7879**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Time to CV death	Overall HR 0.91 (0.76, 1.09) SUBGROUP No CKD HR 0.76 (0.55, 1.04) CKD HR 0.99 (0.79, 1.25)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	Interaction p value 0.1667	
Time to all-cause mortality	Overall HR 1.00 (0.87, 1.15) SUBGROUP No CKD HR 0.94 (0.74, 1.18) CKD HR 1.03 (0.87, 1.21) **Interaction p value 0.5118**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause hospitalisation	Overall HR 0.92 (0.85, 0.99) SUBGROUP No CKD HR 0.90 (0.79, 1.02) CKD HR 0.93 (0.84, 1.03) **Interaction p value 0.6653**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Slope of change in eGFR ml/min/1.73m² per year	Overall Difference 2.4 (1.6-3.2) SUBGROUP No CKD Difference 2.4 (1.2-3.5) CKD Difference 2.4 (1.3-3.5) **Interaction p value 0.9748**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Composite renal end point* *Time to first occurrence of (1) chronic dialysis; (2) renal transplantation; (3) sustained reduction of ≥40% in estimated glomerular filtration rate (eGFR); or (4) sustained eGFR <15 mL/min/1.73m2 for patients with baseline eGFR ≥30 mL/min/1.73m2 or <10 mL/min/1.73m2 for patients with baseline eGFR <30 mL/min/1.73m2.	Overall HR 0.95 (0.73,1.24) SUBGROUP No CKD HR 0.92(0.58, 1.48) CKD HR 0.97 (0.71, 1.34) **Interaction p value 0.8572**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Acute kidney injury	Overall HR 0.73 (0.56 – 0.95) SUBGROUP No CKD HR 0.66(0.38, 1.15) CKD HR 0.76 (0.56, 1.02) **Interaction p value 0.6726**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Progression to macroalbuminuria	Overall HR 0.82 (0.68, 0.98) SUBGROUP No CKD HR 0.84(0.64, 1.10) CKD HR 0.80 (0.63, 1.01) **Interaction p value 0.7736**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Siddiqi 2023(28) SUBGROUP of EMPEROR-PRESERVED	SUBGROUP CKD vs NO CKD <u>Prespecified?</u> No, not for this endpoint. <u>Other remarks on methods</u> -For all hazard ratios or treatment differences not included in the testing hierarchy, no adjustment has been made for multiple comparisons, so the intervals should not be used to infer definitive treatment effects. <u>Baseline characteristics</u> eGFR < 60 ml/min: -placebo: 50.2% -empagliflozin: 49.6%

Outcomes
KCCQ CSS at week 52

Kansas City Cardiomyopathy Questionnaire (KCCQ) changes in clinical summary score at 52 weeks	Overall 4.51±0.31 vs 3.18±0.31 Difference 1.32 (0.45-2.19) SUBGROUP No CKD Difference 1.33 (0.07, 2.58) CKD Difference 1.66 (0.47, 2.85) Interaction p value: 0.704	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

12.1.2.2.3 BMI

Anker 2021(26): EMPEROR-P;
Siddiqi 2023(28):
 	
SUBGROUP Of EMPEROR-PRESERVED
	• SUBGROUP BMI>30 vs BMI<30
	• SUBGROUP 4 BMI categories:
	  ○ BMI < 25 kg/m²
	  ○ BMI 25 - <30 kg/m²
	  ○ BMI 30 - <35 kg/m²
	  ○ BMI ≥35 kg/m²
	
	Prespecified:
	• Yes, 15 prespecified subgroups (for analysis of the **primary endpoint**) included diabetes at baseline (yes/no); **BMI at baseline (≥30/<30)**; eGFR at baseline (≥ or < 60 ml/min/1.73m²)
	• No for the other endpoints.
	• Analysis by **5 BMI categories was not prespecified**

Other important methodological remarks:

- The p-values for the subgroup analyses and interaction were not adjusted for multiple comparisons

Baseline characteristics

BMI>30: 2692/5988 (45%)

Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall 415/2997 vs 511/2991 HR 0.79 (0.69-0.90) p<0.001 **SS** BMI <30 223/1654 vs 292/1642 HR 0.74 (0.62-0.88) BMI ≥30 192/1343 vs 219/1349 HR 0.85 (0.70-1.03) Interaction test: not done	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

Outcomes	

KCCQ-CSS Kansas City Cardiomyopathy Questionnaire (KCCQ) changes in clinical summary score at 52 weeks	<u>Overall</u> 4.51±0.31 vs 3.18±0.31 Difference 1.32 (0.45-2.19) <u>BMI < 25 kg/m²</u> 2.40 (1.10, 3.69) vs 1.94 (0.58-3.31) Difference 0.45 (-1.40, 2.31) <u>BMI 25 - <30 kg/m²</u> 3.39 (2.33, 4.46) vs 2.41 (1.36, 3.46) Difference 0.98 (-0.51, 2.47) <u>BMI 30 - <35 kg/m²</u> 5.60 (4.42, 6.77) vs 3.04 (1.84, 4.24) Difference 2.56 (0.88, 4.23) <u>BMI ≥35 kg/m²</u> 6.87 (5.42, 8.32) vs 5.07 (3.69, 6.45) Difference 1.80 (-0.18, 3.78) **Interaction test**: p=0.153	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

KCCQ changes in total symptom score (KCCQ TSS) at 52 weeks	Overall <u>BMI < 25 kg/m²</u> 3.30 (1.91, 4.86) vs 2.10 (0.64-3.57) Difference 1.19 (-0.79, 3.18) <u>BMI 25 - <30 kg/m²</u> 4.30 (3.16, 5.44) vs 3.40 (2.27, 4.52) Difference 0.90 (-0.70, 2.51) <u>BMI 30 - <35 kg/m²</u> 7.69 (6.43, 8.94) vs 4.12 (2.83, 5.41) Difference 3.57 (1.77, 5.36) <u>BMI ≥35 kg/m²</u> 8.70 (7.15, 10.24) vs 6.05 (4.58, 7.53) Difference 2.64 (0.52, 4.76) **Interaction test**: p=0.080	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

KCCQ changes in overall summary score (KCCQ OSS) at 52 weeks	<u>BMI < 25 kg/m²</u> 3.27 (2.00, 4.53) vs 2.57 (1.24-3.91) Difference 0.69 (-1.12, 2.51) <u>BMI 25 - <30 kg/m²</u> 3.69 (2.65, 4.74) vs 3.04 (2.02, 4.07) Difference 0.65 (-0.81, 2.12) <u>BMI 30 - <35 kg/m²</u> 6.14 (5.00, 7.29) vs 3.14 (1.96, 4.32) Difference 3.00 (1.37, 4.64) <u>BMI ≥35 kg/m²</u> 7.35 (5.94, 8.76) vs 5.23 (3.88, 6.57) Difference 2.12 (0.19, 4.06) **Interaction test**: p=0.078	***12.1.2.3 Was the subgroup variable a baseline characteristic?*** ***12.1.2.4 YES*** ***12.1.2.5*** ***12.1.2.6 Was the subgroup hypothesis specified a priori?*** ***12.1.2.7 NO*** ***12.1.2.8*** ***12.1.2.9 Was the test of interaction significant (interaction P <0.05)?*** ***12.1.2.10 NO*** ***12.1.2.11***

12.1.2.12 EMPERIAL (HFpEF/HFrEF)

Ref Abraham 2021(25))	**EMPERIAL** trials EMPERIAL-Reduced and EMPERIAL-Preserved (Effect of EMPagliflozin on ExeRcise ability and HF symptoms In patients with chronic heArt faiLure)
Study details	Design: RCT ; Double-blind, parallel group Duration of follow-up: 12 weeks
n/population	n= EMPERIAL-Reduced: 312 EMPERIAL-Preserved: 315 Mean age: EMPERIAL-Reduced: 69y EMPERIAL-Preserved: 73.5y Inclusion criteria symptomatic (NYHA II-IV) HF diagnosed ≥3 months prior to screening with LVEF ≤40% (EMPERIAL-Reduced) or >40% (EMPERIAL-Preserved) and 6-minute walk test distance (6MWTD) of ≥100 m at baseline and ≤350 m at screening. Exclusion criteria Conditions that preclude exercise testing, systolic blood pressure of <100 mmHg or ≥180 mmHg, or an estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2 Randomization was not stratified.

Intervention/comparison	Empagliflozin 10 mg vs placebo Patients with LVEF ≤40% were required to be on guideline-directed medical therapy.
Outcomes	**Primary outcome:** 6-minute walk test distance change to week 12 **Key secondary outcomes:** Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) Chronic Heart Failure Questionnaire Self-Administered Standardized format (CHQ-SAS) dyspnoea score
Methodological	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: EMPERIAL-Reduced -empagliflozin arm: there was incomplete follow-up for the primary endpoint in 6/156 patients. -Placebo arm: there was incomplete follow-up for the primary endpoint in 10/156 patients. EMPERIAL-Preserved -empagliflozin arm: there was incomplete follow-up for the primary endpoint in 4/158 patients.

	-Placebo arm: there was incomplete follow-up for the primary endpoint in 6/157 patients. ITT: Yes, all randomized participants analysed for efficacy. Sponsor: Boehringer Ingelheim

12.1.2.12.1DM

SUBGROUP Abraham 2021(25))	SUBGROUP DIABETES vs NO DIABETES Several exploratory subgroup analyses were pre-specified in the statistical analysis plan, including analysis by diabetes status. Baseline characteristics EMPERIAL-REduced Diabetes 187/312 (59.9%) EMPERIAL-Preserved Diabetes 161/315 (51.1%)

Outcomes	
Efficacy	

6-minute walk test distance change to week 12 **(primary outcome)**	EMPERIAL-Reduced Overall Difference -4.0 m (-16.0, 6.0) p<0.42 NS As the primary endpoint was non-significant, all secondary endpoints were considered exploratory. SUBGROUP Diabetes Difference -7.0(-21.0 to 7.0) No diabetes Difference -1.0 (-20.0 to 18.0) **Interaction p value**: not performed EMPERIAL-Preserved Overall Difference 4.0 m (-5.0, 13.0) p<0.37 NS SUBGROUP Diabetes Difference --6.0(-6.0 to 20.0) No diabetes	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

	Difference 3.0 (-10.0 to 17.0) **Interaction p value**: not performed	
Safety		
No analysis of safety data by subgroup		

12.2 MRA

12.2.1 Eplerenone vs placebo

12.2.1.1 Emphasis-HF (HFrEF)

Ref Zannad 2011(29) Study details	**EMPHASIS-HF trial** (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) Design: RCT ; Double-blind, parallel group Duration of follow-up: 21 months The trial was stopped prematurely for crossing the prespecified stopping boundary for an overwhelming benefit.
n/population	n= 2737 Mean age: 68 y Inclusion criteria : an age of at least 55 years, NYHA functional class II symptoms, an **ejection fraction of no more than 30% (**or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography), and treatment with an angiotensin-converting–enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or both and a beta-blocker (unless contraindicated) at the recommended dose or maximal tolerated dose. Key exclusion criteria acute myocardial infarction, NYHA class III or IV heart failure, a serum potassium level exceeding 5.0 mmol per liter, an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m2 of body-surface area, a need for a potassium-sparing diuretic, and any other clinically significant, coexisting condition.
Intervention/comparison	eplererone 25-50 mg (depending on eGFR) vs placebo

Outcomes	**Primary outcome** composite of death from cardiovascular causes or a first hospitalization for heart failure **secondary outcomes** hospitalization for heart failure or death from any cause, death from any cause, death from cardiovascular causes, hospitalization for any reason, and hospitalization for heart failure, among others.
Methodology	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -eplerenone arm: there was incomplete follow-up for the primary endpoint in 188/1364 (13.8%) patients. -Placebo arm: there was incomplete follow-up for the primary endpoint in 222/1373 (16.2%) patients. ITT: yes, all randomized participants were analyzed Sponsor: Pfizer

12.2.1.1.1 DM

Ref Ferreira 2021(30)) SUBGROUP of EMPHASIS-HF (Zannad 2011(29))	SUBGROUP DIABETES vs NO DIABETES The consistency of the treatment effect was assessed among 20 prespecified subgroups, including eGFR≥ or <60 mL:min/1.73m²; history of diabetes; for the **primary endpoint** <u>Baseline characteristics</u> Diabetes Eplerenone group 459/1364 (33.7%) Placebo group 400/1373 (29.1%)

Outcomes	
Efficacy	

death from cardiovascular causes or hospitalization for heart failure **(primary outcome)**	Overall **adjusted HR 0.63 (0.54–0.74) <** **p<0.001** **SS** SUBGROUP DM vs no DOM No diabetes HR 0.72 (0.58 to 0.88) Diabetes HR 0.54 (0.42 to 0.70) Interaction p value 0.09	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
HF hospitalization	Overall **HR** 0.58 (0.48 to 0.71) **P<0.001** SUBGROUP DM vs no DOM No diabetes HR 0.65 (0.5 to 0.84) Diabetes HR 0.52 (0.38 to 0.70 Interaction p value 0.27	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

CV Death	Overall **HR** 0.75 (0.6 to 0.93) **P0.01** SUBGROUP DM vs no DOM No diabetes HR 0.77 (0.58 to 1.02) Diabetes HR 0.73 (0.52 to 1.03) Interaction p value 0.80	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause death or all-cause hospitalization	Overall **HR 0.** 0.76 (0.67 to 0.86) **p<0.001** SUBGROUP DM vs no DOM No diabetes HR 0.78 (0.67 to 0.91 Diabetes HR 0.69 (0.57 to 0.85) Interaction p value 0.37	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

All-cause hospitalization	Overall **HR** 0.77 (0.68 to 0.88) **p<0.001** SUBGROUP DM vs no DOM No diabetes HR 0.78 (0.66 to 0.92) Diabetes HR 0.74 (0.60 to 0.92) Interaction p value 0.72	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause death	Overall **HR** 0.76 (0.62 to 0.92) **P 0.007** SUBGROUP DM vs no DOM No diabetes HR 0.77 (0.59 to 0.99) Diabetes HR 0.75 (0.54 to 1.03) Interaction p value 0.91	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		

Hyperkalemia	Overall Placebo: 50/1373 (3.7%) Eplerenone: 109/1364 (8.0%) P <0.001 SUBGROUP DM vs no DOM No diabetes Placebo: 33/971 (3.4%) Eplerenone: 58/903 (6.4%) Diabetes Placebo: 17/398 (4.3%) Eplerenone: 51/457 (11.2%) Interaction p value 0.32	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Hypokalemia	Overall Placebo: 31/1373 (2.3%) Eplerenone: 16/1364 (1.2%) P 0.032 SUBGROUP DM vs no DOM No diabetes Placebo: 21/971 (2.2%) Eplerenone: 11/903 (1.2%) Diabetes Placebo: 10/398 (2.5%) Eplerenone: 5/457 (1.1%) Interaction p value 0.69	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Renal failure	Overall Placebo: 41/1373 (3.0%) Eplerenone: 39/1364 (2.0%) P 0.84 SUBGROUP DM vs no DOM No diabetes Placebo: 23/971 (2.4%) Eplerenone: 18/903 (2.0%) Diabetes Placebo: 18/398 (4.5%) Eplerenone: 21/457 (4.6%) Interaction p value 0.67	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Hypotension	Overall Placebo: 37/1373 (2.7%) Eplerenone: 46/1364 (3.4%) P 0.30 SUBGROUP DM vs no DOM No diabetes Placebo: 30/971 (3.1%) Eplerenone: 33/903 (3.7 %) Diabetes Placebo: 7/398 (1.8%) Eplerenone: 13/457 (2.8%) Interaction p value 0.56	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

12.2.1.1.2 CKD

Zannad 2011(29)) and Ferreira 2019(41): SUBGROUP Of EMPHASIS-HF (Zannad 2011(29))	SUBGROUP CKD vs no CKD The consistency of the treatment effect was assessed among 20 prespecified subgroups, including eGFR≥ or <60 mL/min/1.73m²; history of diabetes. The target dose of eplerenone/placebo was stratified at randomization according to estimated glomerular filtration rate (eGFR): 50mg/day if **eGFR ≥50ml/min/1.73m²** and 25mg/day if **eGFR 30-49ml/min/1.73m².** The stratification was prespecified, the subgroup analysis according to eGFR**≥50ml/min/1.73m²** and **eGFR 30-49ml/min/1.73m²** was not. . SUBGROUP eGFR≥ vs <60 mL/min/1.73m² <u>Baseline characteristics</u> eGFR <60 mL/min/1.73m² Eplerenone group 439/1364 (32.2%) Placebo group 473/1373 (34.5%) SUBGROUP eGFR≥ vs <50 mL/min/1.73m²

Baseline characteristics
eGFR <50 mL/min/1.73m²
Eplerenone group 618/1364 (33.7%)
Placebo group 544/1373 (29.1%)

Outcomes		
Efficacy		
death from cardiovascular causes or hospitalization for heart failure **(primary outcome)**	Overall **adjusted HR 0.63 (0.54–0.74)** **p<0.001** **SS** SUBGROUP eGFR≥ vs <60 mL/min/1.73m HR not reported Interaction p value 0.50	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
	SUBGROUP eGFR≥ vs <50 mL/min/1.73m eGFR ≥ 50 mL/min/1.73m HR 0.58 (0.45-0.74) eGFR <50 mL/min/1.73m HR 0.62 (0.49-0.78) Interaction p value 0.89	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?**

		NO

12.2.1.1.3 BMI

Olivier 2017(51)

SUBGROUP
Of EMPHASIS-HF

- SUBGROUP BMI≥30 vs BMI<30
- SUBGROUP NWC (normal waist circumference) vs HWC (high waist circumference)
  (i.e. < 102 cm for men and <88 cm for women and HWC for high WC group i.e. abdominal obesity with WC≥ 102 cm for men and ≥88 cm for women)

Prespecified:

Not prespecified.The consistency of the treatment effect was assessed among 20 prespecified subgroups, not including BMI or waist circumference.

Baseline characteristics

2737 patients randomized; 2579 included in WC analysis; 2722 included in BMI analysis

BMI>30: 739/2722 (27%)

HWC: 1295/2579 (50%)

Outcomes		
Efficacy		
Composite outcome cardiovascular mortality or HF hospitalization (primary outcome)	Overall 229/1287 vs 335/1292 HR 0.63 (0.52-0.75) p<0.0001 **SS** Normal waist circumference 137/644 vs 169/640 HR 0.77 (0.61-0.98) p=0.03 High waist circumference 92/643 vs 166/652 HR 0.48 (0.37-0.63) P<0.0001 **Interaction test: p=0.01**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** YES

	BMI < 30 193/975 vs 271/1008 HR 0.69 (0.57-0.83) p= 0.0001 BMI ≥ 30 54/383 vs 85/356 HR 0.49 (0.35-0.71) p= 0.0001 Interaction test: p=0.11	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause mortality	Overall 160/1287 vs 201/1292 HR 0.76 (0.61-0.95) p= 0.01 **SS** Normal waist circumference 97/644 vs 107/640 HR 0.87 (0.66-1.16) p=0.35 High waist circumference 63/643 vs 94/652 HR 0.62 (0.44-0.87) p=0.005	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	Interaction test: p=0.13	
	BMI < 30 135/975 vs 170/1008 HR 0.75 (0.59-0.95) p= 0.02 BMI ≥ 30 35/383 vs 43/356 HR 0.68 (0.43-1.08) p= 0.11 Interaction test: p=0.73	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Cardiovascular death	Overall 136/1287 vs 175/1292 HR 0.73 (0.58-0.93) p= 0.009 **SS** Normal waist circumference 83/644 vs 91/640 HR 0.87 (0.64-1.18) p=0.38 High waist circumference 53/643 vs 84/652 HR 0.58 (0.40-0.83) p=0.003 Interaction test: p=0.09	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
	BMI < 30 116/975 vs 149/1008 HR 0.73 (0.57-0.94) p= 0.02 BMI ≥ 30 30/383 vs 36/356 HR 0.68 (0.43-1.08) p= 0.19 Interaction test: p=0.93	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Hospitalization for HF	Overall 151/1287 vs 238/1292 HR 0.59 (0.48-0.73) p<0.0001 **SS** Normal waist circumference 89/644 vs 118/640 HR 0.71 (0.53-0.95) p=0.02 High waist circumference 62/643 vs 120/652 HR 0.48 (0.35-0.66) p<0.0001 Interaction test: p=0.07	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
	BMI < 30 129/975 vs 194/1008 HR 0.62 (0.49-0.77) p< 0.0001 BMI ≥ 30 34/383 vs 59/356 HR 0.47 (0.30-0.71) p= 0.0004	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	Interaction test: p=0.25	
Safety		
Hyperkalaemia	See table S2 below	
Hypokalaemia	See table S2 below	
Renal failure	See table S2 below	
Hypotension	See table S2 below	

Table S2 Selected investigator-reported adverse events and those leading to permanent withdrawal of the study drug, according to study groups*

	Adverse events						
	NWC			HWC			
Events	Placebo (N=640)	Eplerenone (N=642)	P	Placebo (N=649)	Eplerenone (N=641)	P	p of interaction
	No. of patients (%)			*No. of patients (%)*			
All events	480 (75.0)	467 (72.7)	0.37	479 (73.8)	458 (71.5)	0.35	0.99
Hyperkalaemia	23 (3.6)	59 (9.2)	<0.0001	25 (3.9)	45 (7.0)	0.01	0.31
Hypokalaemia	15 (2.3)	6 (0.9)	0.05	13 (2.0)	8 (1.3)	0.38	0.50
Renal failure	23 (3.6)	20 (3.1)	0.65	17 (2.6)	16 (2.5)	1.00	0.83
Hypotension	17 (2.7)	23 (3.6)	0.42	15 (2.3)	18 (2.8)	0.60	0.82
	Adverse events leading to study-drug withdrawal						
	NWC			HWC			
Events	Placebo (N=640)	Eplerenone (N=642)	P	Placebo (N=649)	Eplerenone (N=641)	P	p of interaction
	No. of patients (%)			*No. of patients (%)*			

All events	93 (14.5)	101 (15.7)	0.59	112 (17.3)	74 (11.5)	0.004	0.01
Hyperkalemia	5 (0.8)	9 (1.4)	0.42	7 (1.1)	6 (0.9)	1.00	0.35
Hypokalaemia	1 (0.2)	0 (0.0)	0.50	1 (0.2)	0 (0.0)	1.00	-
Renal failure	2 (0.3)	2 (0.3)	1.00	3 (0.5)	1 (0.2)	0.62	0.48
Hypotension	0 (0.0)	0 (0.0)	1.00	3 (0.5)	0 (0.0)	0.25	0.98

Adverse events

	BMI< 30			**BMI ≥ 30**			
Events	**Placebo** (N=1005)	**Eplerenone** (N=971)	P	**Placebo** (N=355)	**Eplerenone** (N=383)	P	p of interaction
	No. of patients (%)			*No. of patients (%)*			
All events	754 (75.0)	704 (72.5)	0.22	249 (70.1)	274 (71.5)	0.69	0.20
Hyperkalaemia	38 (3.8)	84 (8.7)	<0.0001	12 (3.4)	25 (6.5)	0.06	0.65
Hypokalaemia	24 (2.4)	14 (1.4)	0.14	7 (2.0)	2 (0.5)	0.10	0.34
Renal failure	33 (3.3)	29 (3.0)	0.80	7 (2.0)	10 (2.6)	0.63	0.49
Hypotension	30 (3.0)	39 (4.0)	0.22	7 (2.0)	6 (1.6)	0.78	0.38

Adverse events leading to study-drug withdrawal

	BMI< 30			**BMI ≥ 30**			
Events	**Placebo** (N=1005)	**Eplerenone** (N=971)	P	**Placebo** (N=355)	**Eplerenone** (N=383)	P	p of interaction
	No. of patients (%)			*No. of patients (%)*			
All events	171 (17.0)	143 (14.7)	0.18	50 (14.1)	44 (11.5)	0.32	0.81
Hyperkalaemia	12 (1.2)	14 (1.4)	0.70	0 (0.0)	1 (0.3)	1.00	-
Hypokalaemia	3 (0.3)	0 (0.0)	0.25	0 (0.0)	0 (0.0)	1.00	-
Renal failure	3 (0.3)	2 (0.2)	1.00	2 (0.6)	2 (0.5)	1.00	0.83
Hypotension	3 (0.3)	0 (0.0)	0.25	0 (0.0)	0 (0.0)	1.00	-

BMI, body mass index expressed in kg/m^2; WC, waist circumference with NWC for normal WC group i.e. < 102 cm for men and <88 cm for women and HWC for high WC group i.e. abdominal obesity with WC≥ 102 cm for men and ≥88 cm for women. * Patients who had received at least one dose of the study drug were included in the safety analysis. P values were calculated on the basis of the number of patients. When convergence problem were encountered for the p of interaction calculation, results were summarized by "-"

12.2.1.2 J-EMPHASIS (HFrEF)

Tsutsui 2017(31)	**J-EMPHASIS-HF**
Study details	Design: RCT ; Double-blind, parallel group Duration of follow-up: Median duration in eplerenone group: 862 days Median duration in placebo group: 859 days
n/population	n= 221 Mean age: 68.7y Inclusion criteria Japanese patients ≥55 years of age who had chronic HF of either ischemic or non-ischemic etiology (duration ≥4 weeks); symptoms of NYHA functional class II or higher; **left ventricular ejection fraction (LVEF) ≤30% (**or ≤35% in addition to QRS duration >130ms on ECG); and treatment with ACE inhibitor, ARB, β-blocker, or diuretic. Key exclusion criteria acute myocardial infarction or stroke within 30 days prior to randomization, serum potassium level >5.0mEq/L, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 within 24 h prior to randomization, need for a potassium-sparing diuretic such as spironolactone, and any other clinically significant coexisting conditions. Randomization was stratificatied by NYHA functional class (II and III/IV) at randomization and eGFR (30 to <50mL/min/1.73 m² and ≥50mL/min/1.73m2) within 24h before randomization

Intervention/comparison	eplererone 25-50 mg (depending on eGFR) vs placebo
Outcomes	**Primary outcome:** composite of death from cardiovascular causes or hospitalization for HF (first occurrence). **Secondary end points** death from any cause; death from cardiovascular causes; hospitalization for any cause; hospitalization for HF; hospitalization for cardiovascular cause; hospitalization for worsening renal function; hospitalization for hyperkalemia; addition or increase of HF medication due to worsening HF; stroke; myocardial infarction; a composite of death from cardiovascular causes, hospitalization for HF, or addition or increase of HF medication due to worsening HF; composite of death from any cause or hospitalization for any cause; and composite of death from HF or hospitalization for HF.
Methodology	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -eplerenone arm: the study drug was discontinued in 36/111 patients. Number of patients with incomplete follow-up not reported. -Placebo arm: the study drug was discontinued in 36/110 patients. Number of patients with incomplete follow-up not reported. ITT: yes (The primary and secondary outcomes were analyzed using data from all patients who underwent randomization

Sponsor:
Pfizer

12.2.1.2.1 DM

Tsutsui 2017(31)

SUBGROUP DIABETES vs NO DIABETES

<u>Prespecified?</u>
Yes, “The consistency of the treatment effect was assessed among prespecified subgroups.”

<u>Baseline characteristics</u>
Diabetes 88/221 (39.8%)

Outcomes	
Efficacy	

death from cardiovascular causes or hospitalization for heart failure **(primary outcome)**	Overall HR 0.85 (0.53 to 1.36)* P 0.50 **To demonstrate efficacy, the consistency of results with the EMPHASIS-HF study was predefined as a point estimate of the hazard ratio <1 in the primary endpoint of death from cardiovascular causes or hospitalization for HF* SUBGROUP Diabetes No HR reported No diabetes No HR reported **Interaction p value**: 0.64	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

12.2.1.2.2 CKD

Tsutsui 2017(31)	SUBGROUP CKD vs NO CKD Prespecified? Yes, "The consistency of the treatment effect was assessed among prespecified subgroups." Baseline characteristics CKD (eGFR<60 ml/min/m²) 133/221 (60.2%)

Outcomes		
Efficacy		
death from cardiovascular causes or hospitalization for heart failure **(primary outcome)**	<u>Overall</u> HR 0.85 (0.53 to 1.36)* P 0.50 **To demonstrate efficacy, the consistency of results with the EMPHASIS-HF study was predefined as a point estimate of the hazard ratio <1 in the primary endpoint of death from cardiovascular causes or hospitalization for HF* SUBGROUP eGFR<60 ml/min/1.73m² vs ≥60 ml/min/1.73m² SUBGROUP <u>CKD</u> No HR reported <u>No CKD</u> No HR reported **Interaction p value**: 0.39	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

12.2.1.3 EPHESUS (HFrEF)

Pitt 2003(32)	**EPHESUS** (Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)
Study details	Design: RCT ; Double-blind, parallel group Duration of follow-up: median 16 months
n/population	n= 6642 Mean age: 64y Inclusion criteria 3 to 14 days after acute myocardial infarction: acute myocardial infarction as documented according to standard criteria; left ventricular dysfunction as documented by a left ventricular **ejection fraction of 40 percent or lower** on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute myocardial infarction and before randomization; and heart failure as documented by the presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound. In patients with diabetes who met the criteria for left ventricular dysfunction after acute myocardial infarction, symptoms of heart failure did not have to be demonstrated Key exclusion criteria use of potassium-sparing diuretics, a serum creatinine concentration of more than 2.5 mg per deciliter (220 µmol per liter), and a serum potassium concentration of more than 5.0 mmol per liter before randomization. T Randomization was stratificatied by clinical site
Intervention/comparison	eplererone (25 mg per day initially, titrated to a maximum of 50 mg per day) vs placebo Patients received optimal medical therapy, which could include ACE inhibitors, angiotensin-receptor blockers, diuretics, and beta-blockers, as well as coronary reperfusion therapy
Outcomes	**Primary outcome:**

Methodology	• Death from any cause (no. of patients) • Death from cardiovascular causes or hospitalization for cardiovascular events (including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia) (no. of patients) **Secondary end points** • death from cardiovascular causes • death from any cause or any hospitalization. RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -eplerenone arm: Number of patients with incomplete follow-up 10/3319 patients -Placebo arm: Number of patients with incomplete follow-up 7/3313 patients ITT: 10 randomized patients were excluded from the analysis before unblinding because of problems with the quality of the data at one center (modified ITT) Sponsor: Pharmacia

12.2.1.3.1 DM

Pitt 2003(32) SUBGROUP of EPHESUS	SUBGROUP DIABETES vs NO DIABETES <u>Prespecified?</u> Subgroup analyses for the two primary end points were prespecified <u>Baseline characteristics</u> Diabetes 32%

Outcomes		
Efficacy		
death from any cause **(primary outcome)**	<u>Overall</u> RR 0.85 (0.75–0.96) P 0.008 SS SUBGROUP <u>Diabetes</u> No RR reported <u>No diabetes</u> No RR reported **Interaction p value**: 0.35	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

Death from cardiovascular causes or hospitalization for cardiovascular events **(primary outcome)**	Overall RR 0.87 (0.79–0.95) P 0.002 SS SUBGROUP Diabetes No HR reported No diabetes No HR reported **Interaction p value**: 0.59	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

12.2.2 Spironolactone vs placebo

12.2.2.1 RALES (HFrEF)

Pitt 1999 (42)**(** Study details	**RALES** (Randomized Aldactone Evaluation Study) Design: RCT ; Double-blind, parallel group Duration of follow-up: mean 24 months

n/population	n= 1663 Mean age: 65 y Inclusion criteria New York Heart Association (NYHA) class IV heart failure within the six months before enrollment and were in NYHA class III or IV at the time of enrollment, had been given a diagnosis of heart failure at least six weeks before enrollment, were being treated with an ACE inhibitor (if tolerated) and a loop diuretic, and had a left ventricular ejection fraction of no more than 35 percent within the six months before enrollment (with no clinically significant intercurrent event). Key exclusion criteria primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to left ventricular systolic heart failure), congenital heart disease, unstable angina, primary hepatic failure, active cancer, or any life-threatening disease (other than heart failure). Patients who had undergone heart transplantation or were awaiting the procedure were also ineligible. Other criteria for exclusion were a serum creatinine concentration of more than 2.5 mg per deciliter (221 µmol per liter) and a serum potassium concentration of more than 5.0 mmol per liter.
Intervention/comparison	spironolactone 25 mg (up to 50 mg) vs placebo
Outcomes	**Primary outcome:** All-cause mortality **Secondary end points** death from cardiac causes, hospitalization for cardiac causes, the combined incidence of death from cardiac causes or hospitalization for cardiac causes, and a change in the NYHA class.
Methodology	RANDO: Adequate

	ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -spironolactone arm: 222/822 patients discontinued treatment. Follow-up was complete. -Placebo arm: 211/841 patients discontinued treatment. Follow-up was complete. ITT: yes (analysis of the primary end point included all randomized patients) Sponsor: Searle <u>Other important remarks</u> The trial was discontinued early, after a mean follow-up period of 24 months, because an interim analysis determined that spironolactone was efficacious (observed effect of spironolactone on the primary endpoint exceeded the prespecified critical z value)

12.2.2.1.1 CKD

Pitt 1999 (42)**(**	SUBGROUP CKD vs NO CKD (median creatinine ≥ or < 1.2 mg/dL) <u>Prespecified?</u>

SUBGROUP of RALES trial	Yes, for primary endpoint The effect of spironolactone was also assessed with the use of six prerandomization variables: left ventricular ejection fraction, the cause of heart failure, **the serum creatinine concentration**, age, the use of ACE inhibitors, and the use of digitalis. <u>Baseline characteristics</u> Proportion of patients with median creatinine ≥ 1.2 mg/dL not reported

Outcomes		
Efficacy		
All-cause mortality **(primary outcome)**	<u>Overall</u> RR 0.70 (95% CI 0.60 to 0.82) P <0.001 SS SUBGROUP <u>CKD</u> RR not reported <u>No CKD</u> RR not reported **Interaction p value**: not reported Described narratively as being consistent with overall results among all subgroups	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

Vardeny 2012(43) SUBGROUP of RALES trial	SUBGROUP CKD vs NO CKD (eGFR ≥ or < 60 ml/min/1.73m²) <u>Prespecified?</u> No <u>Baseline characteristics</u> Proportion of patients with eGFR < 60 ml/min/1.73m²: 792/1658 (47.8%)

Outcomes		
Efficacy		
All-cause mortality **(primary outcome)**	<u>Overall</u> RR 0.70 (95% CI 0.60 to 0.82) P <0.001 SS SUBGROUP <u>CKD</u> RR 0.71 (0.57–0.90) <u>No CKD</u> RR 0.68 (0.56–0.84) **Interaction p value**: not reported Described narratively as being consistent with overall results	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Death or HF hospital stay	Overall RR 0.68 (95% CI 0.59 to 0.78) P <0.001 SS SUBGROUP CKD RR 0.64 (0.52–0.77) No CKD RR 0.67 (0.56–0.81) **Interaction p value**: not reported Described narratively as being consistent with overall results	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

12.2.2.2 TOPCAT (HFpEF)

Pitt 2014(33)	**TOPCAT trial** (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist)
Study details	Design: RCT ; Double-blind, parallel group Duration of follow-up: mean 3.3 years
n/population	n= 3445

	Median age: 68.7y Inclusion criteria 50 years of age or older at least one sign and at least one symptom of heart failure on a prespecified list of clinically defined signs and symptoms, a left ventricular **ejection fraction of 45% or more** as measured at the local site by means of echocardiography or radionuclide ventriculography, controlled systolic blood pressure (defined as a target systolic blood pressure of <140 mm Hg or ≤160 mm Hg if the patient was taking three or more medications to control blood pressure), and a serum potassium level of less than 5.0 mmol per liter. In addition, eligible patients had a history of hospitalization within the previous 12 months, with management of heart failure a major component of the care provided (not adjudicated by the clinical-events adjudication committee), or an elevated natriuretic peptide level within 60 days before randomization Key exclusion criteria severe systemic illness with a life expectancy of less than 3 years, severe renal dysfunction (an estimated glomerular filtration rate [GFR] of <30 ml per minute per 1.73 m2 of body-surface area or a serum creatinine level that was ≥2.5 mg per deciliter [221 µmol per liter]), and specific coexisting conditions, medications, or acute events Randomization was stratified according to whether patients were enrolled on the basis of the first criterion (designated the hospitalization stratum) or the second criterion (designated the BNP stratum).
Intervention/comparison	Spironolactone 15-45 mg vs placebo
Outcomes	**Primary outcome:** a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **Secondary end points**

	death from any cause, hospitalization for any cause, hyperkalemia (potassium level, ≥5.5 mmol per liter), hypokalemia (potassium level, <3.5 mmol per liter), an elevated serum creatinine level (≥2 times the baseline value and above the upper limit of the normal range), and a serum creatinine level of 3.0 mg per deciliter (265 µmol per liter) or higher
Methodology	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: -spironolactone arm: there was incomplete follow-up in 67/1722 (3.9%) patients. -Placebo arm: there was incomplete follow-up in 65/1723 (3.8%)patients. ITT: yes (all randomized patients were included in all analyses according to the intention-to-treat principle) Sponsor: National Heart, Lung, and Blood Institute

12.2.2.2.1 DM

Pitt 2014(33) SUBGROUP of TOPCAT trial	SUBGROUP DIABETES (insulin-treated) vs DIABETES (non-insulin-treated) vs NO DIABETES <u>Prespecified?</u> Yes A total of 22 prespecified subgroup analyses were conducted for the primary outcome (including Diabetes mellitus status: No; Yes, insulin-treated; Yes, non-insulin treated) <u>Other remarks on methods</u> No adjustments for multiplicity were made <u>Baseline characteristics</u> Diabetes, insulin-treated 175/3445 (5.0%) Diabetes, non-insulin-treated 152/3445 (4.4%)

Outcomes	
Efficacy	

composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **(primary outcome)**	Overall HR 0.89 (0.77-1.04) SUBGROUP Diabetes-insulin HR 0.80 (0.59-1.07) Diabetes-no insulin HR 0.90 (0.65-1.23) No diabetes HR 0.90 (0.73-1.11) **Interaction p value**: 0.82	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

12.2.2.2.2 CKD

Pitt 2014(33) SUBGROUP of	SUBGROUP CKD vs NO CKD (eGFR ≥ or < 60 mL/min:1.73m²) Prespecified?

TOPCAT trial	Yes A total of 22 prespecified subgroup analyses were conducted for the primary outcome (including eGFR ≥ or < 60 mL/min:1.73m²) <u>Other remarks on methods</u> No adjustments for multiplicity were made <u>Baseline characteristics</u> eGFR ≥ 60 mL/min:1.73m²: 320/3445 (9.3%)

Outcomes		
Efficacy		
composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **(primary outcome)**	<u>Overall</u> HR 0.89 (0.77-1.04) SUBGROUP <u>CKD</u> HR 0.82 (0.66-1.02) <u>No CKD</u> HR 0.95 (0.77-1.17) **Interaction p value**: 0.34	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

12.2.2.3 TOPCAT Americas (HFpEF)

12.2.2.3.1 OG

Pfeffer 2014(44)	**Post-hoc regional subgroup of** **TOPCAT trial** (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) **This post hoc analysis was based on the observation of an unusually large difference in the placebo event rates between the sites conducting TOPCAT in the 4 countries in the Americas compared with those in Russia and Georgia.**
Study details	Design: RCT ; Double-blind, parallel group; post hoc subgroup Duration of follow-up: mean 2.9 years
n/population	n= 1767 Median age: 72y Inclusion criteria TOPCAT participants from the Americas (United States, Canada, Brazil, and Argentina) Exclusion TOPCAT participants from Russia/Georgia
Intervention/comparison	Spironolactone 15-45 mg vs placebo

Outcomes	**Primary outcome:** a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **Secondary end points** death from any cause, hospitalization for any cause, hyperkalemia (potassium level, ≥5.5 mmol per liter), hypokalemia (potassium level, <3.5 mmol per liter), an elevated serum creatinine level (≥2 times the baseline value and above the upper limit of the normal range), and a serum creatinine level of 3.0 mg per deciliter (265 µmol per liter) or higher
Methodology	RANDO: Unclear ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: There was incomplete follow-up in 37/1767 (2.1%) patients. ITT: yes (all randomized patients were included in all analyses according to the intention-to-treat principle) Sponsor: National Heart, Lung, and Blood Institute

All analyses reported in the primary TOPCAT article were repeated separately for the 2 regions, the Americas (United States, Canada, Brazil, and Argentina) and Russia/Georgia

Outcomes		
Efficacy		
composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **(primary outcome)**	Overall HR 0.89 (0.77-1.04) SUBGROUP AMERICAS HR 0.82 (0.66-1.02) GEORGIA/RUSSIA HR 1.10(0.79–1.51) **Interaction p value**: 0.12	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

12.2.2.3.2 CKD

Beldhuis 2019(45) SUBGROUP eGFR ≥ 60 mL/min/1.73m² versus 45-<60 mL/min/1.73m² versus <45 mL/min/1.73m²;

SUBGROUP of TOPCAT AMERICAS trial	<u>Prespecified?</u> No; post hoc subgroup analysis of post hoc subgroup analysis (TOPCAT Americas) <u>Other remarks on methods</u> No adjustments for multiplicity were made <u>Baseline characteristics</u> eGFR ≥ 60 mL/min/1.73m²: 823/1767 (47%) 45-<60 mL/min/1.73m²: 533/1767 (30%) <45 mL/min/1.73m² : 411/1767 (23%)

Outcomes		
Efficacy		
composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure **(primary outcome)**	<u>Overall</u> HR 0.82(0.69–0.98) p 0.026 SUBGROUP <u>eGFR ≥ 60 mL/min/1.73m²:</u> HR 0.66 (0.50 to 0.88) <u>eGFR 45-<60 mL/min/1.73m²:</u> HR 0.99 (0.73 to 1.36) <u>eGFR <45 mL/min/1.73m</u>	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	HR 0.89 (0.66 to 1.21) **Interaction p value**: 0.13	

12.2.2.3.3 BMI

Elkholey 2021(13) SUBGROUP of TOPCAT AMERICAS trial	• SUBGROUP BMI≥30 vs BMI<30 • SUBGROUP NWC (normal waist circumference) vs HWC (high waist circumference) *(i.e. < 102 cm for men and <88 cm for women and HWC for high WC group i.e. abdominal obesity with WC≥ 102 cm for men and ≥88 cm for women)* <u>Prespecified?</u> No; post hoc subgroup analysis of post hoc subgroup analysis (TOPCAT Americas) <u>Other remarks on methods</u> • No adjustments for multiplicity were made • Multivariate associations were adjusted for all patient characteristics that differed significantly between BMI and WC categories in frequency or magnitude with backwards elimination until a parsimonious model was achieved. Hazard ratios (HR) and 95% confidence

intervals (CI) were calculated. P values <0.05 were considered statistically significant for the main effect. Due to the low power of interaction tests, a p value <0.1 was considered statistically for the interaction effect, as previously described. **Note of bibliography group: we used p<0.05 to consider statically significant interactions**.

- When BMI was treated as a continuous variable, there was a linear association between BMI and the effect of spironolactone vs. placebo for the primary outcome and cardiovascular death, with the benefit becoming statistically significant at 33kg/m2 and 30kg/m2, respectively (Figure 4). A similar linear association between the effect of spironolactone and BMI as a continuous variable was observed for all cause death and HF hospitalizations, but none of them reached statistical significance.
- When waist circumference was treated as a continuous variable, there was a linear association between WC and the effect of spironolactone vs. placebo for the primary outcome, cardiovascular death and HF hospitalizations, with the benefit becoming statistically significant at 109cm, 103cm and 123cm, respectively. The association between the effect of spironolactone and waist circumference as a continuous variable for all-cause death did not reach statistical significance.

<u>Baseline characteristics</u>
TOPCAT Americas cohort:n= 1767
n= 1751 in BMI analysis and n=1643 in WC analysis

BMI>30: 1135/1751 (66%)

HWC: /1643 (79%)

Outcomes		
Efficacy		
Composite of cardiovascular death, HF hospitalization, or aborted cardiac arrest (primary outcome)	<u>Overall in TOPCAT Americas cohort</u> BMI-analysis HR 1.003 (0.98-1.44); p= 0.987 WC analysis	

	HR 1.03 (0.73-1.47); p= 0.834	
	<u>BMI ≥30</u> HR 0.62 (0.46-0.83) p=0.001 <u>BMI<30</u> HR 0.95 (0.62-1.44) p=0.796 **Interaction test**: p=0.056	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
	<u>High waist circumference</u> HR 0.74 (0.56-0.98) p=0.035 <u>Normal waist circumference</u> HR 0.64 (0.36-1.15) p=0.134 **Interaction test**: p=0.930	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Cardiovascular death	<u>Overall in TOPCAT Americas cohort</u> BMI-analysis HR 0.81 (0.58-1.02); p= 0.417 WC analysis HR 0.84 (0.50-1.40); p= 0.513	

	BMI ≥30 HR 0.48 (0.28-0.83) p=0.009 BMI<30 HR 0.74 (0.42-1.33) p=0.313 **Interaction test**: p=0.412	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
	High waist circumference HR 0.54 (0.34-0.87) p=0.012 Normal waist circumference HR 0.65 (0.29-1.47) p=0.299 **Interaction test**: p=0.887	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause death	Overall in TOPCAT Americas cohort BMI-analysis HR 0.85 (0.69-1.06); p= 0.411 WC analysis HR 1.05 (0.72-1.55); p= 0.76	
	BMI ≥30 HR 0.76 (0.52-1.11)	**Was the subgroup variable a baseline characteristic?** YES

	p=0.157 BMI<30 HR 0.84 (0.55-1.30) p=0.438 **Interaction test**: p=0.734	**Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
	High waist circumference HR 0.78 (0.56-1.10) p=0.155 Normal waist circumference HR 0.83 (0.46-1.52) p=0.554 **Interaction test**: p=0.757	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
HF hospitalizations	Overall in TOPCAT Americas cohort BMI-analysis HR 1.11 (0.77-1.62); p= 0.574 WC analysis HR 1.30 (0.84-2.02; p= 0.221	
	BMI ≥30 HR 0.64 (0.47-0.88) p=0.007	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?**

	BMI<30 HR 1.03 (0.61-1.73) p=0.913 **Interaction test**: p=0.130	NO **Was the test of interaction significant (interaction P <0.05)?** NO
	High waist circumference HR 0.78 (0.57-1.06) p=0.112 Normal waist circumference HR 0.61 (0.28-1.33) p=0.211 **Interaction test**: p=0.990	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

12.3 ARNI

12.3.1 Sacubitril/valsartan vs enalapril

12.3.1.1 PARADIGM-HF (HFrEF)

Ref McMurray 2014(14)	Effect of angiotensin neprilysin inhibition **versus enalapril** on morbidity and mortality in heart failure with a reduced ejection fraction
Study details	Design: RCT ; Double-blind, parallel group, active-controlled study Event driven, outcomes trial (end of the study will occur when the prespecified number of patients (2410) achieves the primary composite endpoint). Duration of follow-up: up to 43 months. • single-blind run-in period during which all patients received enalapril (2 weeks) followed by a single-blind run-in period during which all patients received sacubitril/valsartan (4 to 6 weeks) • double-blind treatment for active treatment tablet along with placebo matching the opposite treatment The dose of the study drug could be reduced in patients who had unacceptable side effects at target doses. Treatment taken in addition to their conventional concomitant therapy (except for ACEI or ARB, which will be substituted with study drug).
n/population	n= 4399 (4187 vs 4212) <u>Mean age:</u> Sacubitril/valsartan: 63.8 ± 11.5 Enalapril: 63.8± 11.3 <u>Inclusion criteria</u> Patients 18 years or older with a diagnosis of CHF NYHA class II-IV **and reduced ejection fraction:**

	• LVEF ≤ 40% • and BNP ≥ 150 pg/ml (NT-proBNP ≥ 600 pg/ml) OR BNP ≥ 100 pg/mL (NT-proBNP ≥ 400 pg/ml) and a hospitalization for HF within the last 12 monthsLVEF ≤ 40% , Must be **on an ACEI or an ARB** at a stable dose of at least enalapril 10 mg/d or equivalent for at least 4 weeks **and treated with a β-blocker**, unless contraindicated or not tolerated, at a stable dose for at least 4 weeks. <u>Key exclusion criteria</u> Requirement of treatment with **both** ACEIs and ARBs, Acute decompensated HF, Symptomatic hypotension and/or a systolic blood pressure (SBP) < 100 mmHg, **Estimated GFR < 30 mL/min/1.73m2, or > 25% decline in eGFR**, Serum potassium > 5.2 mmol/L, Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty, **History of severe pulmonary disease**, untreated ventricular arrhythmia with syncopal episodes, Symptomatic bradycardia or second or third degree heart block without a pacemaker <u>Subgroups:</u> A full set of subgroups will be looked at for subgroup analysis for the **primary endpoint and its components** Subgroups considered are: Age group (<65 vs ≥65 years; <75 vs ≥75 years), Gender, Race, Region, **Baseline eGFR (<60 vs ≥60 mL/min/1.73 m2), Diabetic at baseline (yes/no),** Baseline SBP (three groups: ≤110 mmHg; >110 mmHg and ≤140 mmHg; >140 mmHg), Ischemic cardiomyopathy at baseline vs non-ischemic cardiomyopathy at baseline, Baseline LVEF (≤median vs >median), Baseline BNP (≤median vs > median), AF at baseline (yes/no), Hypertension at baseline (yes/no), Prior RAAS drug at screening (ACEI/ARB), Use of β-blocker at baseline (yes/no), Use of aldosterone antagonists at baseline (yes/no), Previous hospitalization for HF (yes/no),Time since diagnosis of HF (three groups: ≤1 year; 1 to 5 years; >5 years). Diabetes 3784/8399 CKD 2745/8399 In principle, there will be no adjustment for multiple comparisons for subgroup analyses.
Intervention/comparison	sacubitril/valsartan 200mg 2x/d vs enalapril 10 mg 2x/d

	in addition to guideline directed standard of care therapy
Outcomes	**Primary outcome:** time to composite endpoint of CV death or first hospitalization for heart failure, **study powered for death from CV cause** **Secondary end points** • Change of clinical summary score for HF symptoms and physical limitations (as assessed by KCCQ) at 8 months • time to all-cause mortality • time to composite renal endpoint of (1) a 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline, (2) >30 mL/min/1.73 m2 decline in eGFR relative to baseline, or (3) reaching end stage renal disease (ESRD). • time to a new onset of atrial fibrillation **Exploratory assessments** Composite CV mortality and morbidity (CV death, hospitalization for HF, non-fatal MI, non-fatal stroke or resuscitated sudden death) • Non-fatal stroke • Non-fatal MI • Resuscitated sudden death • Days alive out of the hospital at 12 months • Decline in eGFR (eGFR slope) • Time to study treatment failure for HF • Change in clinical composite score (assessed by NYHA classification and patient global assessment) at 8 months • New onset of AF • New onset diabetes • Improvement in quality of life (KCCQ and EQ-5D) • Coronary revascularization procedures • BNP, NT-proBNP • Other predefined biomarkers • Days/stays in ICU • ER visits • Steady state plasma concentrations of valsartan, AHU377, and LBQ657 immediately before the study drug dose and at 0.5-2 hours and 3-5 hours after study drug dose, AEs and SAEs • Sitting systolic (SBP) and sitting diastolic BP (DBP) • Heart rate • Symptomatic hypotension • Angioedema • Laboratory values • Hyperkalemia • Renal dysfunction • ECG changes
Methodology	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes

	Assessors: yes FOLLOW-UP: -sacubitril/valsartan arm: 746/4187 (17.8%) discontinued, 11 lost to follow up -enalapril arm: 833/4212 (19.8%) discontinued, 9 lost to follow up ITT: yes <u>Sponsor:</u> Novartis

Outcomes		
Efficacy		
Composite of cardiovascular death or first hospital admission for heart failure **(primary outcome)**	<u>Overall</u> n 4187 vs 4212 HR: 0·80 95% CI: 0·73–0·87 P < 0·001 SS in favour of sacubitril/valsartan SUBGROUP **<u>Diabetes</u>** n 1451 vs 1456 HR: N.R. **<u>No diabetes</u>** 2736 vs 2756 HR: N.R.	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **YES** **Was the test of interaction significant (interaction P <0.05)?** **NO**

	Interaction p value: 0.40 SUBGROUP **<u>CKD</u>** n 1541 vs 1520 HR: N.R. **<u>No CKD</u>** 2646 vs 2692 HR: N.R. **Interaction p value**: 0.91	
Cardiovascular death	<u>Overall</u> n 4187 vs 4212 HR: 0·80 95% CI: 0·71–0·89 P < 0·001 SS in favour of sacubitril/valsartan SUBGROUP **<u>Diabetes</u>** n 1451 vs 1456 HR: N.R. **<u>No diabetes</u>** 2736 vs 2756 HR: N.R. **Interaction p value**: 0.052	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **YES** **Was the test of interaction significant (interaction P <0.05)?** **NO**

	(reduced effect with sacubitril/valsartan) SUBGROUP **<u>CKD</u>** n 1541 vs 1520 HR: N.R. **<u>No CKD</u>** 2646 vs 2692 HR: N.R. **Interaction p value**: 0.73	

<u>Author's conclusion</u>

The effect of sacubitril/valsartan was consistent across all prespecified subgroups.

12.3.1.1.1 DB

Ref Packer 2018 (34) From PARADIGM-HF	SUBGROUP DIABETES vs NO DIABETES **<u>Prespecified?</u>** This comparison was one of the 12 **prespecified exploratory outcomes** in the final statistical plan, but the **analysis for the effect of diabetes was not specifically described**. <u>Baseline characteristics</u> Diabetes 3784/8399 Patients were identified as having diabetes if they reported a history of diabetes (by medical record review or self-report) or had an **HbA1c concentration of 6,5%** (48 mmol/mol) or more at screening. The difference between patients with and those without diabetes in the rate of decline in eGFR was not attributable to baseline differences in their clinical characteristics; the more rapid deterioration in eGFR in patients with diabetes was apparent even after adjustment for baseline systolic blood pressure, serum creatinine, BMI, NTproBNP, functional class of heart failure, history of

hypertension or myocardial infarction, or use of drug treatments at baseline, parameters that statistically significantly differed between groups.

Outcomes		
Efficacy		
eGFR decline (mL/min per 1·73m² per year) **(expl. outcome)**	Overall –1.3 *vs* –1.8 MD: 0·4 (95% CI: 0·3 to 0·6) P < 0·0001 SS in favour of sacubitril/valsartan SUBGROUP Diabetes n 1907 vs 1877 -1.7 vs -2.3 MD: 0.6 (95% CI: 0.4–0.8) p<0·0001 No diabetes n 2280 vs 2335 -1.0 vs -1.3 MD: 0.3 (95% CI: 0.2–0.5) p=0·0002 **Interaction p value**: **0.038**	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **NO** **Was the test of interaction significant (interaction P <0.05)?** **YES**
Safety		

Not reported by DM subgroup	

Other remarks

Authors of the study have also reported several biomarkers based on treatment assignment in diabetes and no diabetes groups. As following our methodology we only mention clinical endpoints, these different outcomes were not included in the present report.

Conclusion of authors:

"The presence of type 2 diabetes accelerates the deterioration of renal function that occurs
over time in patients with chronic heart failure. This deleterious effect is attenuated by neprilysin inhibition. The benefits of neprilysin inhibition occurred in patients already receiving high doses of drugs that block the renin-angiotensin system and have favourable effects on the course of diabetic nephropathy."
"the magnitude of the benefit was larger in patients with versus those without diabetes… The greater effect of neprilysin inhibition in patients with diabetes could not be explained by the effects of treatment on the course of heart failure or on HbA1c."

Ref Seferovic 2017 (35) From PARADIGM-HF	SUBGROUP DIABETES vs NO DIABETES **Prespecified?** No, **post-hoc analysis** from PARADIGM-HF Baseline characteristics Diabetes 3778/ 8399 Subset of patients who reported a history of diabetes, had **HbA1c concentrations of 6·5% or more**, or both at screening. (98%) had type 2 diabetes 2896 (77%) patients had a previous diagnosis of diabetes with a median duration of 3·5 years, and a screening mean HbA1c of 7·44% (SD 1·55). More than half of the patients (57%) used antihyperglycaemic therapy at screening, mostly metformin, sulfonylureas, and insulin. There were no significant differences in HbA1c concentrations between randomised groups at screening.

Outcomes		
Efficacy		
Composite **primary outcome** of cardiovascular death or first hospital admission for heart failure	<u>Overall</u> HR: 0·80 95% CI: 0·73–0·87 P < 0·001 SS in favour of sacubitril/valsartan SUBGROUP <u>Diabetes</u> n 1904 vs 1874 HR: 0·84 95% CI: 0·74–0·95 p=0·0043 <u>No diabetes</u> Not reported **Interaction p value**: 0.40 (from the original study)	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **YES** **Was the test of interaction significant (interaction P <0.05)?** **NO**

Cardiovascular death **(secondary outcome)**	<u>Overall (full analysis)</u> HR: 0·80 95% CI: 0·71–0·89 P < 0·001 SS in favour of sacubitril/valsartan No row data reported: **"suggested attenuated benefit of sacubitril/valsartan in patients with diabetes"** **Interaction p value: 0.052** Within this subgroup, the proportional hazards assumption was violated. In particular, significant violations of the constant HR assumption are detectable when comparing the first 12 months vs the subsequent follow-up. SUBGROUP **restricted to 12 months** <u>Diabetes</u> n 1904 vs 1874 HR: 0·74 95% CI: 0·56–0·97 p=0·03 <u>No diabetes</u> HR=0.83 95% CI: 0.68-1.03 p=0.09	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **NO (analysis restricted to 12 months)** **Was the test of interaction significant (interaction P <0.05)?** **N.R. (analysis restricted to 12 months**

	Interaction p value: Not Reported	
HbA1c concentration (%) 3 years **(expl. outcome)**	<u>Overall</u> MD: -0.01 (95% CI: -0.04 to 0.01) p=0.29 NS SUBGROUP <u>Diabetes</u> MD: -0.14 (95% CI: -0.23 to -0.06) p=0.0055 <u>No diabetes</u> MD:0.00 (95% CI: -0.05 to 0.06) p=0.87 **Interaction p value**: Not reported	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **NO** **Was the test of interaction significant (interaction P <0.05)?** **N.R.**

Incident diabetes	SUBGROUP No diabetes 39/2741 (1%) vs 44/2762 p=0·63 **Interaction p value**: N.A.	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **NO** **Was the test of interaction significant (interaction P <0.05)?** **N.A.**
New initiation of insulin therapy (Incidence rate (per 100 person-years)) 3 years	SUBGROUP Diabetes 3.5 (2.9–4.2) vs 5·0 (4.2–5.8) HR: 0.71 (95% CI: 0.56 to 0.90) p=0·0052 **Interaction p value**: N.A.	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **NO** **Was the test of interaction significant (interaction P <0.05)?** **N.A.**

BMI (kg/m2)	Overall Data not reported SUBGROUP Diabetes MD: 0.28 (95% CI: 0.14 to 0.91) p=<0·0001 **Interaction p value**: Not reported	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **NO** **Was the test of interaction significant (interaction P <0.05)?** **N.R.**

Other remarks

Authors also analysed changes in triglycerides, HDL cholesterol. As these are not clinical end points data are not reported in this document.

Author's conclusion

The HbA1c reduction from sacubitril/valsartan was apparent only in patients identified as having diabetes at screening, with no treatment effect seen in patients without diabetes.

However, within the diabetes cohort, there was no significant relationship between screening HbA1c concentrations and the magnitude of the treatment effect.

In summary, we found that treatment with sacubitril/valsartan resulted in improved glycaemic control as shown by lower HbA1c concentrations compared with patients treated with enalapril for patients with diabetes and HFrEF.

These post-hoc findings should be considered hypothesis-generating

12.3.1.1.2 CKD

Ref Damman 2018(46)	SUBGROUP CKD vs NO CKD **Prespecified?**

FROM PARADIGM-HF	The differential effect of sacubitril/valsartan **on the primary outcome in the subgroups of patients with and without CKD (eGFR <60 ml/min/1.73 m2)** at baseline was a pre-specified subgroup analysis. <u>Baseline characteristics</u> CKD 2745/8399 (33%) mean eGFR (overall population) was 70.20 ml/min/1.73 m2 1,872 patients had a screening UACR measurement, the median UACR was 1.0 mg/mmol (IQR: 0.4 to 3.2 mg/mmol) and a total of 441 patients (24%) had microalbuminuria or macroalbuminuria.

Outcomes		
Efficacy		
Composite of CV death or first HF Hospitalization **(Primary outcome)**	<u>Overall</u> n 4187 vs 4212 914 vs 1117 HR: 0.80 (95% CI: 0.73 to 0.87) P < 0.001 SS in favour of sacubitril valsartan SUBGROUP <u>CKD</u> n 1333 vs 1412 368 vs 465 HR: 0.79 (95% CI: 0.69–0.90) <u>No CKD</u> n 2854 vs 2800	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

	556 vs 552 HR: 0.81 (95% CI: 0.73–0.91) **Interaction p value**: 0.70 SUBGROUP KDOQI stage I (eGFR > 90) HR: 0.77 (95% CI: 0.61–0.98) KDOQI stage II (eGFR 60-90) HR: 0.83 (95% CI: 0.73–0.94) KDOQI stage IIIa (eGFR 45-60) HR: 0.73 (95% CI: 0.61–0.86) KDOQI stage IIIb/IV/V (eGFR <45) HR: 0.90 (95% CI: 0.72–1.13) **Interaction p value**: 0.96	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

CV death	Overall n 4187 vs 4212 558 vs 693 HR: 0.80 (95% CI: 0.71 to 0.89) P < 0.001 SS in favour of sacubitril valsartan SUBGROUP CKD n 1333 vs 1412 211 vs 291 HR: 0.76 (95% CI: 0.63–0.90) No CKD n 2854 vs 2800 347 vs 402 HR: 0.84 (95% CI: 0.72–0.96) **Interaction p value**: 0.39 SUBGROUP KDOQI stage I (eGFR > 90) HR: 0.69 (95% CI: 0.52–0.93) KDOQI stage II (eGFR 60-90) HR: 0.89 (95% CI: 0.75–1.05) KDOQI stage IIIa (eGFR 45-60) HR: 0.71 (95% CI: 0.57–0.90) KDOQI stage IIIb/IV/V (eGFR <45)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO **Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	HR: 0.82 (95% CI: 0.62–1.09) **Interaction p value**: 0.75	
First HF hospitalization	<u>Overall</u> n 4187 vs 4212 537 vs 658 HR: 0.79 (95% CI: 0.71 to 0.89) P < 0.001 SS in favour of sacubitril valsartan SUBGROUP <u>CKD</u> n 1333 vs 1412 223 vs 288 HR: 0.79 (95% CI: 0.67–0.95) <u>No CKD</u> n 2854 vs 2800 314 vs 370	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

	HR: 0.81 (95% CI: 0.70–0.94) **Interaction p value**: 0.83 SUBGROUP <u>KDOQI stage I (eGFR > 90)</u> HR: 0.84 (95% CI: 0.61–1.16) <u>KDOQI stage II (eGFR 60-90)</u> HR: 0.80 (95% CI: 0.68–0.95) <u>KDOQI stage IIIa (eGFR 45-60)</u> HR: 0.74 (95% CI: 0.60–0.95) <u>KDOQI stage IIIb/IV/V (eGFR <45)</u> HR: 0.89 (95% CI: 0.66–1.19) **Interaction p value**: 0.55	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause mortality **(Secondary outcome)**	<u>Overall</u> n 4187 vs 4212 711 vs 835 HR: 0.84 (95% CI: 0.76 to 0.93) P <0.001 SS in favour of sacubitril valsartan SUBGROUP <u>CKD</u> n 1333 vs 1412 269 vs 354 HR: 0.79 (95% CI: 0.68–0.93)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	No CKD n 2854 vs 2800 442 vs 481 HR: 0.89 (95% CI: 0.78–1.01) **Interaction p value**: 0.27 SUBGROUP KDOQI stage I (eGFR > 90) HR : 0.77 (95% CI: 0.59–0.1) KDOQI stage II (eGFR 60-90) HR : 0.93 (95% CI: 0.80–1.08) KDOQI stage IIIa (eGFR 45-60) HR : 0.71 (95% CI: 0.58–0.87) KDOQI stage IIIb/IV/V (eGFR <45) HR : 0.93 (95% CI: 0.72–1.19) **Interaction p value**: 0.90	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Composite renal outcome (first occurrence of any of: 1) a 50% decline in eGFR relative to baseline; 2) >30 ml/min/1.73 m2 decline in eGFR relative to baseline to <60 ml/min/1.73 m2; or 3) reaching end-stage renal disease) **(secondary outcome)**	Overall n 4187 vs 4212 94 vs 108 HR: 0.86 (95% CI : 0.65 to 1.13) P = 0.29 **NS** SUBGROUP CKD n 1333 vs 1412 22 vs 36 HR : 0.64 (95% CI: 0.37–1.08) No CKD n 2854 vs 2800 72 vs 72 HR : 0.97 (95% CI: 0.70–1.34) **Interaction p value**: 0.19 SUBGROUP KDOQI stage I (eGFR > 90) HR : 1.06 (95% CI: 0.54–2.1) KDOQI stage II (eGFR 60-90) HR : 0.94 (95% CI: 0.65–1.36) KDOQI stage IIIa (eGFR 45-60) HR : 0.60 (95% CI: 0.32–1.14) KDOQI stage IIIb/IV/V (eGFR <45)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO **Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	HR : 0.70 (95% CI: 0.27–1.84) **Interaction p value**: 0.37	
Decline in eGFR ml/min/1.73 m2/year **(exploratory outcome)**	<u>Overall</u> n 4187 vs 4212 -1.61 (95%CI: -1.77 to-1.44) vs -2.04 (95% CI:-2.21 to -1.88) MD (95% CI): 0.44 (0.21 to 0.67) p < 0.001 SS in favour of sacubitril/valsartan SUBGROUP <u>CKD</u> n 1333 vs 1412 -0.80 (-1.05 to -0.54) vs -1.55 (-1.81 to -1.30) MD (95% CI): 0.76 (0.40 to 1.12) <u>No CKD</u>	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	n 2854 vs 2800 -1.98 (-2.18 to -1.78) vs -2.29 (-2.50 to -2.08) MD (95% CI): 0.31 (0.02 to 0.60) **Interaction p value**: 0.54	
Post hoc composite renal outcome (either a 50% decrease in the eGFR from baseline or reaching end-stage renal disease)	<u>Overall</u> n 4187 vs 4212 37 vs 58 HR: 0.63 (95% CI: 0.42–0.95) P = 0.028 SS in favour of sacubitril/valsartan SUBGROUP <u>CKD</u> n 1333 vs 1412 16 vs 26 HR: 0.64 (95% CI: 0.34–1.19) <u>No CKD</u> n 2854 vs 2800 21 vs 32 HR: 0.63 (95% CI: 0.36–1.10) **Interaction p value**: 0.97	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		

serum creatinine ≥ 2.5mg/dl during follow-up	Overall n 4187 vs 4212 188 vs 139 OR: 0.73 (95% CI: 0.59–0.92) P = 0.007 SS in favour of sacubitril valsartan SUBGROUP CKD 251 in total No CKD 76 in total **Interaction p value**: NS (data not reported)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
serum creatinine ≥ 3.0 mg/dl during follow-up	Overall n 4187 vs 4212 63 vs 83 OR: 0.76 (95% CI: 0.55–1.06) P = 0.10 NS SUBGROUP CKD 76 in total	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	No CKD 45 in total **Interaction p value**: NS (data not reported)	
Patients stopping drug for reason other than mortality	Overall n 4187 vs 4212 746 vs 833 HR: 0.89 (95% CI: 0.80–0.98) P = 0.018 SS in favour of sacubitril/valsartan SUBGROUP CKD n 1333 vs 1412 324 vs 355 HR: 0.97 (95% CI: 0.84–1.13) No CKD n 2854 vs 2800 422 vs 478 HR: 0.84 (95% CI: 0.74–0.96)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	Interaction p value: 0.18	
Patient stopping drug because of renal adverse effect	Overall n 4187 vs 4212 29 vs 59 HR: 0.49 (95% CI: 0.31–0.76) P = 0.0022 SS in favour of sacubitril/valsartan SUBGROUP CKD n 1333 vs 1412 15 vs 36 HR: 0.43 (95% CI: 0.24–0.80) No CKD n 2854 vs 2800 14 vs 23 HR: 0.59 (95% CI: 0.30–1.15) **Interaction p value**: 0.52	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Other remarks

Authors of the studies have also report the differential effects of sacubitril/valsartan in other subgroup based on distinct kidney function parameters such UACR, micro or macro-albuminuria values. As the current definition of CKD is based on eGFR values, and **because these other delineations were not prespecified**, we only reported the differential effects of sacubitril/valsartan in patients with or without CKD defined as eGFR < 60 ml/min/1.73 m2.

In the study authors reported that worsening of UACR category was associated with a higher risk of the pre-specified composite renal endpoint in the enalapril arm (HR: 4.21; 95% CI:
1.66 to 10.68), but not in the sacubitril/valsartan arm (HR: 0.50; 95% CI: 0.07 to 3.77; p = 0.06 for
interaction). Similarly, a 25% increase in the UACR was associated with a higher risk of the renal
composite endpoint in the enalapril arm (HR: 2.53; 95% CI: 1.09 to 5.84), but not in the sacubitril/valsartan arm (HR: 0.28; 95% CI: 0.08 to 1.01; p = 0.005 for interaction).

Conclusion of the authors

Compared with enalapril, sacubitril/valsartan led to a slower rate of decrease in the eGFR and improved cardiovascular outcomes, even in patients with chronic kidney disease, despite causing a modest increase in UACR.
The benefit of sacubitril/valsartan over enalapril was consistent across the components
of the primary endpoint, and for all-cause mortality, in patients with and without CKD, and for any stages of CKD, including stage 3b CKD.

12.3.1.1.3 COPD

Ref Ehteshami-Afshar 2021(53) FROM PARADIGM-HF	SUBGROUP COPD vs NO COPD **Prespecified?** No according to the original study protocol Baseline characteristics COPD 1080/8399 (12.9%) The presence of COPD was recorded using a yes/no check box by individual site investigators at study entry. **Investigator-derived diagnosis** of COPD was obtained from hospital records, pulmonary function if available, and questioning the patient. No prespecified criteria were defined in the investigator brochure. Furthermore, investigators were not required

to document previous smoking history.

Patients with COPD were older than patients without COPD (mean 67 versus 63 years; *P*<0.001), with similar left ventricular ejection fraction, but higher NT-proBNP (1741 pg/mL versus 1591 pg/mL), worse functional class (NYHA III/IV 37% versus 23%), KCCQ–Clinical Summary Score (73 versus 81), more congestion and comorbidity. Inequalities in the treatment of patients with COPD were apparent only for beta-blockers, and of lesser magnitude than previous studies

The estimated hazard ratios (HRs) were adjusted for all the important predictors of mortality and morbidity using Cox proportional hazards models. Models were adjusted for region, treatment, age, sex, race, systolic blood pressure, heart rate, body mass index, serum creatinine, clinical features of heart failure (LVEF, NT-proBNP [log]), New York Heart Association class, hypertension, diabetes mellitus, atrial fibrillation, hospitalization for HF, myocardial infarction, stroke, and duration of HF.

Finally, in this analysis, no adjustment was made for multiplicity.

Outcomes		
Efficacy		
Composite of CV death or HF Hospitalization (Primary outcome)	<u>Overall</u> n 4187 vs 4212 914 vs 1117 HR: 0.80 (95% CI: 0.73 to 0.87) P <0.001 SS in favour of sacubitril valsartan SUBGROUP <u>COPD</u> n 550 vs 530 156 vs 164 HR: 0.92 (95% CI: 0.74–0.1.15)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	<u>No COPD</u> n 3637 vs 3682 758 vs 953 HR: 0.78 (95% CI: 0.71–0.85) **Interaction p value**: 0.171	
CV death	<u>Overall</u> n 4187 vs 4212 558 vs 693 HR: 0.80 (95% CI: 0.71 to 0.89) P <0.001 SS in favour of sacubitril/valsartan SUBGROUP <u>COPD</u> n 550 vs 530 91 vs 95 HR: 0.94 (95% CI: 0.71–1.26) <u>No COPD</u> n 3637 vs 3682 467 vs 598 HR: 0.78 (95% CI: 0.69–0.88) **Interaction p value**: 0.241	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

First HF hospitalization	<u>Overall</u> n 4187 vs 4212 537 vs 658 HR: 0.79 (95% CI : 0.71 to 0.89) P <0.001 SS in favour of sacubitril valsartan SUBGROUP <u>COPD</u> n 550 vs 530 103 vs 113 HR: 0.88 (95% CI: 0.67–1.15) <u>No COPD</u> n 3637 vs 3682 435 vs 545 HR: 0.78 (95% CI: 0.69–0.88) **Interaction p value**: 0.430	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause mortality (Secondary outcome)	<u>Overall</u> n 4187 vs 4212 711 vs 835 HR: 0.84 (95% CI: 0.76 to 0.93) P <0.001 SS in favour of sacubitril valsartan	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?**

	SUBGROUP <u>COPD</u> n 550 vs 530 115 vs 126 HR: 0.90 (95% CI: 0.70–1.16) <u>No COPD</u> n 3637 vs 3682 596 vs 709 HR: 0.84 (95% CI: 0.75–0.93) **Interaction p value**: 0.638	NO
CV hospitalization	<u>Overall</u> Not reported SUBGROUP <u>COPD</u> n 550 vs 530 211 vs 198 HR: 1.05 (95% CI: 086–1.27) <u>No COPD</u> n 3637 vs 3682 999 vs 1146 HR: 0.85 (95% CI: 0.78–0.92) **Interaction p value**: 0.055	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

Mean change in KCCQ at 8 mo (SE) **(secondary outcome)**	Overall −2.99±0.36 vs −4.63±0.36 MD: 1.64 (0.63–2.65) p = 0.001 SS in favour of sacubitril/valsartan SUBGROUP COPD n 550 vs 530 −4.47 (0.89) vs −5.63 (0.91) MD: 1.16 (1.27) No COPD n 3637 vs 3682 −2.74 (0.35) vs −4.50 (0.35) MD : 1.76 (0.5) **Interaction p value**: 0.449	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
Not reported by COPD subgroup		

Other remarks

Authors of the study have also reported NT-proBNP at 8 months based on treatment in both groups. We have not report this outcome as following our methodology we only clinical endpoints have to be reported.

Conclusion of the authors

Sacubitril/valsartan was beneficial in this high-risk subgroup.

The benefit of sacubitril/valsartan over enalapril was consistent in patients with and without COPD for all end points.

12.3.2 Sacubitril/valsartan vs valsartan

12.3.2.1 PARAGON-HF (HFpEF)

Ref Solomon 2019 (15)	Effect of angiotensin receptor–neprilysin inhibition vs valsartan in patients with heart failure **with preserved ejection fraction**
Study details	Design: RCT ; Double-blind, parallel group, active-controlled study The trial will be event driven with a target total of 1847 primary endpoint events to be accrued Minimum follow-up is to be 2 years and 2 months. • single-blind run-in phase: patient received valsartan 40 mg or 80 mg twice daily for one to two weeks. If started on 40 mg twice daily, the dose was increased to 80 mg twice daily after one week. If patients tolerated valsartan, they were switched to sacubitril/valsartan 49/51mg twice daily for 2 to 4 weeks. • double-blind treatment with sacubitril–valsartan (target dose, 97 mg + 103 mg twice daily) or valsartan (target dose, 160 mg twice daily), if no unacceptable side effects and laboratory values within prespecified safety criteria within run-in phase. **Renin–angiotensin system inhibitors other than mineralocorticoid-receptor antagonists were discontinued** before the run-in period, but all other background medications were continued. The dose of the trial drugs could be adjusted down if the target dose led to unacceptable side effects.
n/population	n= 4822 4796 for efficacy analysis (2407 vs 2389) <u>Mean age:</u> Sacubitril/valsartan: 72.7±8.3

Valsartan: 72.8±8.5

The characteristics of the patients at baseline were balanced between the two treatment groups, except for **small differences in ischemic cause of heart failure (899 (37.4%) vs 824 (34.5%)) and mineralocorticoid-receptor antagonist use (592 (24.6%) 647 (27.1%)).**

Inclusion criteria

patients **50 years or older** with signs and symptoms of heart failure, NYHA class II to IV, an **ejection fraction of 45% or higher** within the previous 6 months, elevated level of natriuretic peptides, structural heart disease, and **diuretic therapy**.

Key exclusion criteria

symptomatic hypotension (or a systolic blood pressure <110 mm Hg at screening or <100 mm Hg at random treatment assignment); **an eGFR of <30 mL/min/1.73 m2 at screening or <25 mL/min/1.73 m2 at randomization**, or a decrease >35% in eGFR between screening and randomization; hyperkalemia (serum potassium >5.2 mmol/L at screening or >5.4 mmol/L at random treatment assignment); acute coronary syndrome (including MI), cardiac surgery, current acute decompensated HF requiring augmented therapy with diuretic agents, vasodilator agents, and/or inotropic drugs; patients who require treatment **with 2 or more of the following: an ACEI, an ARB, or a renin inhibitor;** a known history of angioedema; probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e., dyspnea, fatigue), such as **significant pulmonary disease (including primary pulmonary hypertension)**, anemia, or **obesity**. **Specifically, patients with the following are excluded: a) Severe pulmonary disease including COPD** or b) Hemoglobin 40 kg/m2; patients with SBP ≥180 mm Hg at visit 1, patients with a cardiac resynchronization therapy device; history of pancreatic injury, pancreatitis, or evidence of impaired pancreatic function/injury within the past 5 years; evidence of hepatic disease.

Subgroups:

Subgroup analyses will be performed for the primary and secondary endpoints based on the FAS.

	Age group (median) • Gender (male/female) • Race • Region • **Diabetic at baseline (yes/no)** • Baseline SBP (≤median vs. >median) • Baseline LVEF (≤median vs. >median) • Baseline NT-proBNP (≤median vs. > median) • **Baseline eGFR (< vs > 60 mL/min/1.73 m2)** • AF at baseline (yes/no) • Use of MRAs at baseline (yes/no) • ACEI intolerant patients (yes/no). 12 prespecified subgroups were analyzed individually and then in a multivariable model. Data are shown from a multivariable model that accounted for all potential interactions.
Intervention/comparison	Sacubitril 97 mg/valsartan 103 mg 2x/d vs valsartan 160 mg 2x/d
Outcomes	**The primary outcome:** composite of total (first and recurrent) hospitalizations for heart failure and death from cardiovascular causes. Remarks: In all the proposed analyses, it is acknowledged that the **study will not be powered to achieve statistically significant results for the CV death.** The inference on the total HF hospitalizations can only be made when both the composite endpoint and the total HF hospitalizations itself showed statistically positive results. **Secondary outcomes:** • change of clinical summary score KCCQ at 8 • the change in NYHA class from at 8 months; • the first occurrence of a decline in renal function (decrease in the estimated glomerular filtration rate of ≥50%, development of end-stage renal disease, or death due to renal failure) in a time-to-event analysis (composite renal outcome) • death from any cause Hypotension, renal dysfunction, hyperkalemia, and angioedema were prespecified **adverse events of interest** **Exploratory assessments** 1.Change in clinical composite assessment (NYHA, global patient assessment, and clinical events defined as CV death and HF hospitalization) at 8 months; 2. Patient global assessment at 8 months; 3. Changes from baseline in health-related QoL

	(assessed by the total score, clinical summary score, and individual scores of the sub-domains from the KCCQ and assessments of the EQ-5D for health status); 4. Number of HF events per-subject; 5. Number of worsening HF events or CV death per-patient; 6. Number of all-cause hospitalizations per-subject and number of cause specific hospitalizations per-subject; 7. Number of days alive and out of hospital at 12 months; 8. Time from randomization to first occurrence of composite renal endpoint event, defined as either: a. Renal death, or b. a 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline, or c. >30 mL/min/1.73 m2 decline in eGFR relative to baseline to a value below 60 mL/min/1.73 m2 , or d. reaching end stage renal disease (ESRD); 9. Rate of change in eGFR (eGFR slope); 10. Time from randomization to NODM; 11. Number of days staying in intensive care unit (ICU), number of re-hospitalizations for HF, and number of ER visits for HF; 12. Indicator of 30 day HF rehospitalization (after a prior HF hospitalization); 13. Number of rehospitalizations within 30 days after discharge; 14. Time between HF hospital readmissions; 15. Changes in pre-specified biomarkers (e.g., vascular, renal, collagen, metabolism, and inflammatory biomarkers) from baseline to predefined time-points (in a subset of patients); 16. Variables to characterize the PK of valsartan, AHU377, and LBQ657 at steady-state in patients receiving LCZ696 using population modeling and/or non-compartmental based methods; 17. Time to onset of recurrent AF for patients with a history of AF but without AF at Visit 1; 18. Indicator of presence of AF >5 minutes (for the AF substudy); 19. AF burden measured by the total AF duration over total monitoring time; 20. Echocardiographic parameters in a subset of patients.
Methodology	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 7 patients who had withdrawn consent and 2 patients who were lost to follow-up. ITT: yes <u>Sponsor:</u>

Novartis

Outcomes		
Efficacy		
Composite of total hospitalizations for heart failure and death from cardiovascular causes. **(primary outcome)**	Overall n 2407 vs 4389 RR: 0.87 95% CI: 0.75-1.01 P =0.06 **NS** SUBGROUP Diabetes RR: 0.89 95% CI: 0.74−1.09 No diabetes RR: 0.84 95% CI: 0.68−1.04 **Interaction p value**: NS, no data reported SUBGROUP CKD RR: 0.79 95% CI: 0.66−95 No CKD	**Was the subgroup variable a baseline characteristic?** **YES** **Was the subgroup hypothesis specified a priori?** **YES** **Was the test of interaction significant (interaction P <0.05)?** **NO**

	RR: 1.01 95% CI: 0.80−1.27 **Interaction p value**: NS, no data reported	

Author's conclusion

The primary composite outcome of total hospitalizations for heart failure and death from cardiovascular causes did not differ significantly between the two groups.

Because this difference did not meet the predetermined level of statistical significance, **subsequent analyses were considered to be exploratory**.

Of the 12 prespecified subgroups, 2 showed possible heterogeneity of treatment effect, with a suggestion of benefit in patients with an ejection fraction in the lower part (45 to 57%) of the range studied and in women.

12.3.2.1.1 CKD

Ref Mc Causland 2020(47) FROM PARAGON-HF	SUBGROUP CKD vs NO CKD **Prespecified?** Yes , according to original study protocol. **BUT:** Although the composite renal outcome was a key prespecified secondary outcome of PARAGON-HF, the trial **was not primarily powered** for analyses of the individual renal components, or for the assessment of differences in eGFR decline. Baseline characteristics differential effect of sacubitril/valsartan on the renal outcome, according to the baseline eGFR **(< or > 60 ml/min/1.73 m2,** eGFR at randomization, modeled as a continuous variable). At baseline, the mean eGFR was 63±19 mL.min–1.1.73 m–2 and **47% of patients had an eGFR <60 mL·min–1·1.73 m–2.** Overall, at baseline, patients with eGFR <60 mL.min–1.1.73 m–2 (mean 47±8

mL.min–1.1.73 m–2) were more likely to be older, female, have a history of diabetes mellitus, atrial fibrillation or previous stroke, to be taking a diuretic, and
have marginally higher ejection fraction and N-terminal pro-B-type natriuretic peptide; they were less likely to be taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and had lower systolic blood pressure.

The mean eGFR was 77±14 mL.min–1.1.73 m–2 in those with baseline eGFR > 60 mL·min–1.1.73 m–2.

Patients had similar characteristics according to treatment assignment within
these subgroups.

All analyses were performed at the nominal α-level of 0.05 without correction for multiple hypothesis testing.

Outcomes		
Efficacy		
Composite renal outcome (defined as either: (1) > 50% decline in eGFR relative to baseline; (2) development of end-stage renal disease; or (3) death attributable to renal causes) **(Secondary outcome)**	Overall n 2407 vs 2389 33 (1.4%) vs 64 (2.7%) HR: 0.50 (95% CI: 0.33 to 0.77) P = 0.001 SS in favour of sacubitril valsartan SUBGROUP CKD n 1177 vs 1164 16 (1.4%) vs 32 (2.7%) HR : 0.50 (95% CI: 0.28–0.92) No CKD	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO

	n 1211 vs 1243 17 (1.4%) vs 32 (2.6%) HR : 0.51 (95% CI: 0.29–0.93) **Interaction p value**: 0.92	
>50% decline in eGFR	<u>Overall</u> n 2407 vs 2389 27 (1.1%) vs 60 (2.5%) HR: 0.44 (95% CI: 0.28 to 0.69) SS in favour of sacubitril valsartan SUBGROUP <u>CKD</u> n 1177 vs 1164 11 (1.0%) vs 28 (2.4%) HR : 0.39 (95% CI: 0.20–0.79) <u>No CKD</u> n 1211 vs 1243 16 (1.3%) vs 32 (2.6%)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	HR : 0.48 (95% CI: 0.27–0.88) **Interaction p value**: NS, data not provided	
End-stage renal disease	<u>Overall</u> n 2407 vs 2389 7 (0.3%) vs 12 (0.5%) HR : 0.58 (95% CI : 0.23 to 1.47) NS SUBGROUP <u>CKD</u> n 1177 vs 1164 6 (0.5%) vs 12 (1.0%) HR : 0.51 (95% CI: 0.19–0.1.35) <u>No CKD</u> n 1211 vs 1243 1 vs 0 HR : N.A.	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	Interaction p value: NS, data not provided	
Safety		
Adverse events requiring study drug discontinuation, serious adverse events, and permanent discontinuation attributable to renal impairment were more common among those with baseline eGFR <60 mL·min–1·1.73 m–2 (versus eGFR > 60 mL·min–1·1.73 m–2).		**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?**

	SUBGROUP CKD more hypotensive events, fewer episodes of elevated serum creatinine >2 mg/dL, and no difference in the frequency of hyperkalemic events with sacubitril/valsartan vs valsartan NO CKD fewer episodes of serum creatinine > 2 mg/dL or hyperkalemia > 6 mmol/L with sacubitril/valsartan vs valsartan	Not Reported

Author's conclusion

In summary, in patients with HFpEF enrolled in the PARAGON-HF trial, treatment with sacubitril/valsartan resulted in fewer adverse renal events and slower decline in eGFR, despite a higher frequency of hypotensive events. It is notable that these renal benefits appear
to extend across the spectrum of baseline renal function, providing an important therapeutic option to slow renal function decline in patients with HFpEF.

12.3.2.1.2 COPD

Ref Mooney 2021 (54)	SUBGROUP COPD vs NO COPD **Prespecified?** No according to the original study protocol Baseline characteristics Among 4796 patients included in the primary efficacy analysis of PARAGON-HF,

5 did not have information on COPD status.
COPD 670 (14%)/4791 with information about COPD status.

The presence of COPD was recorded using a yes/no check box on the case-report
form completed by site investigators at study entry. **The protocol specifically excluded patients with "severe COPD,"** defined as COPD requiring home oxygen, chronic nebulizer, or chronic oral steroid therapy, or resulting in hospitalization for pulmonary decompensation within the prior 12 months.

Patients with COPD were older, less likely to be women, and had a higher heart
rate. Current and prior smoking were more common in patients with COPD than in those without. Patients with COPD were more likely than those without to have a history of coronary heart disease and of stroke. However, they did not
have a higher prevalence of AF or atrial flutter. Patients with COPD had a lower (worse) KCCQ clinical summary score than patients without COPD. Patients with COPD had a higher serum creatinine (100.2 +/- 29.0 µmol/L versus 95.8+/-27.0 µmol/L). The greatest difference in cardiovascular therapy between
patients with and without COPD was in use of beta blockers, diuretic and nitrate prescriptions were more common in patients with COPD. **Patients with COPD had worse functional class (New York Heart Association class III/IV, 24.1% versus 19.1%) and a more frequent history of heart failure hospitalization (54.2% versus 47.1%; *P*<0.001), compared with participants without COPD.**

Outcomes		
Efficacy		
Composite of CV death or total HF Hospitalization **(Primary outcome)**	<u>Overall</u> n 2407 vs 4389 RR: 0.87 95% CI: 0.75-1.01 P =0.06 **NS**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO

	SUBGROUP COPD n 343 vs 327 214 vs 246 HR : 0.83 (95% CI: 0.60–0.1.14) No COPD n 2063 vs 2059 680 vs 762 HR: 0.88 (95% CI: 0.75–1.04) **Interaction p value**: 0.66	**Was the test of interaction significant (interaction P <0.05)?** NO
CV death	Overall n 2407 vs 4389 HR: 0.95 (95% CI: 0.79–1.16) **NS** SUBGROUP COPD n 343 vs 327 46 vs 39 HR : 1.12 (95% CI: 0.73–0.1.72) No COPD n 2063 vs 2059	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	158 vs 173 HR: 0.91 (95% CI: 0.74–1.13) **Interaction p value**: 0.43	
Total HF hospitalization	<u>Overall</u> n 2407 vs 4389 RR: 0.85 (95% CI: 0.72–1.00) **NS** SUBGROUP <u>COPD</u> n 343 vs 327 168 vs 207 HR : 0.77 (95% CI: 0.54–0.1.10) <u>No COPD</u> n 2063 vs 2059 522 vs 589 HR : 0.87 (95% CI: 0.73–1.05) **Interaction p value**: 0.50	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO
All-cause mortality **(Secondary outcome)**	<u>Overall</u> n 2407 vs 4389 342 vs 349 HR: 0.97 (95% CI: 0.84-1.13) **NS**	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO

	SUBGROUP COPD n 343 vs 327 69 vs 76 HR : 0.86 (95% CI: 0.62–1.20) No COPD n 2063 vs 2059 273 vs 272 HR : 1.00 (95% CI: 0.85–1.19) **Interaction p value**: 0.39	**Was the test of interaction significant (interaction P <0.05)?** NO
KCCQ CSS at 8 months **(Secondary outcome)**	Overall n 2407 vs 4389 MD: 1.0 (0.0–2.1) **NS** SUBGROUP COPD n 343 vs 327 MD (SD): 1.30 (1.51) No COPD n 2063 vs 2059 MD (SD): 0.97 (0.51)	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** NO **Was the test of interaction significant (interaction P <0.05)?** NO

	Interaction p value: 0.51	

Author's conclusion

Patients with COPD had worse symptoms, functional limitation, and quality of life, compared with those without, and a higher risk of heart failure hospitalization and cardiovascular death, possibly related to right ventricular enlargement.
Baseline history of COPD did not modify the effect of sacubitril/valsartan compared with valsartan on any prespecified mortality/hospitalization outcome, or on change in KCCQ-CSS.

12.3.2.2 PARAGLIDE

The PARAGLIDE-HF trial demonstrated reductions in natriuretic peptides with sacubitril/valsartan compared with valsartan in patients with heart failure (HF) with mildly reduced or preserved ejection fraction who had a recent worsening HF (WHF) event, but was not adequately powered to examine clinical outcomes.

Included population specifically concerned patients following stabilization in decompensated HFpEF including patient in current hospitalization for WHF (HFpEF decompensation), or within 30 days of discharge following a WHF event (defined as hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics).

Because both the methodological limitations and the restricted population (not in adequation with our first line requirements) this trial has not been reported in the present document.

12.3.3 Sacubitril/valsartan vs standar medical therapy (HFpEF)

12.3.3.1 PARALLAX (HFpEF)

HFpEF

Pieske 2021(36)	**PARALLAX trial** (Prospective Comparison of ARNI vs Comorbidity-Associated Conventional Therapy on Quality of Life and Exercise Capacity)
Study details	Design: RCT ; Double-blind, parallel group Duration of follow-up: 24 weeks
n/population	n= 2572 Mean age: Sacubitril/valsartan group: 72.9y Control: 72.4y Inclusion criteria 45 years or older • with symptomatic heart failure requiring the use of diuretics, New York Heart Association (NYHA) functional class II through IV • elevated plasma NT-proBNP levels (>220 pg/mL for patients in sinus rhythm, and >600 pg/mL for patients with atrial fibrillation or atrial flutter); with evidence of structural heart disease (either left atrial enlargement or left ventricular hypertrophy) as demonstrated by echocardiography • **with an LVEF of 40% or higher** • KCCQ-CSS<75 Key exclusion criteria • Acute coronary syndrome (including myocardial infarction), cardiac surgery, other major cardiovascular surgery, or urgent percutaneous coronary intervention within 3 months prior to screening • Current (within 30 days from Visit 1) use of renin inhibitor(s), dual RAS blockade, or sacubitril/valsartan • Probable alternative diagnoses that could account for the HF symptoms, specifically **severe pulmonary disease**; anemia (Hb <10 g/dL in males, <9.5 g/dL in females); **BMI >40kg/m2** • **eGFR <30 mL/min/1.73m²** at screening

	• Patients with HbA1c >7.5%, not treated for diabetes Randomization was stratified by RAS inhibitor treatment modality: ACE-inhibitor, ARB or neither
Intervention/comparison	Sacubitril/valsartan 97mg/103mg vs standard medical therapy* *active-controlled (for patients taking angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs] prior to recruitment): enalapril 10 mg or valsartan 160 mg; or placebo-controlled (for patients who were naive to a renin angiotensin system [RAS] inhibitors prior to recruitment)
Outcomes	**Primary outcome:** • change in plasma NT-proBNP concentrations from baseline to week 12 • change in the 6-minute walk distance from baseline to week 24 **(in the subgroup of patients with a baseline ability of walk between 100 m and 450 m)** **Secondary end points** mean change from baseline in KCCQ-CSS at week 24, proportion of patients with a 5-point score change in deterioration or improvement at week 24, and change in NYHA functional class
Methodology	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP:

	-sacu/val arm: there was incomplete follow-up for the primary endpoint in 7/1286 patients. (5 misrandomized or misstratified; 2 lost to follow-up) -Placebo arm: there was incomplete follow-up for the primary endpoint in 1/1286 patients. (1 misrandomized) ITT: modified ITT (all validly randomized patients except for those who were misrandomized or misstratified and did not receive any study drug.) Sponsor: Novartis Pharma AG

12.3.3.1.1 DM

Pieske 2021(36) SUBGROUP of PARALLAX trial	SUBGROUP DIABETES vs NO DIABETES (history of diabetes mellitus or HbA1c at screening ≥ 6.5%, no history of diabetes mellitus and HbA1c at screening < 6.5%) <u>Prespecified?</u> Yes, for primary and secondary endpoints <u>Baseline characteristics</u> Diabetes Sacubitril/valsartan group: 566/1281 (44.2%) Control: 589/1285 (45.8%)

Outcomes	
Efficacy	

change in the 6-minute walk distance from baseline to week 24 (in the subgroup of patients with a baseline ability of walk between 100 m and 450 m) *An increase by 30 m was considered as a minimal clinically important difference* **(primary outcome)**	<u>Overall</u> Adj. MD -2.50 m (-8.53 to 3.53) SUBGROUP <u>Diabetes</u> Adj. MD -2.94 m (-11.91 to 6.02) <u>No diabetes</u> Adj. MD -2.34 m (-10.47 to 5.79) **Interaction p value**: 0.92	**Was the subgroup variable a baseline characteristic?** YES **Was the subgroup hypothesis specified a priori?** YES **Was the test of interaction significant (interaction P <0.05)?** NO
Safety		
Not reported by DM subgroup		

13 Appendix. Search strategy

13.1 Search date

The searches were run in MEDLINE via Pubmed on July 8th, 2024.

13.2 HF AND Diabetes

("Heart Failure"[Mesh] OR heart failure*[tiab] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR ((heart[tiab] OR cardia*[tiab] OR myocardial[tiab]) AND (failure[tiab] OR insuffienc*[tiab] OR decompensate*[tiab])))
AND
("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "Mineralocorticoid Receptor Antagonists"[Mesh] OR "sacubitril and valsartan sodium hydrate drug combination"[Supplementary Concept] OR gliflozin*[tiab] OR canagliflozin*[tiab] OR dapagliflozin*[tiab] OR empagliflozin*[tiab] OR ertugliflozin*[tiab] OR spironolacton*[tiab] OR eplerenon*[tiab] OR sacubitril*[tiab] OR SGLT[tiab] OR gliflozin*[tiab] OR MRA[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND
("Diabetes Mellitus, Type 2"[Mesh] OR NIDDM[tiab] OR (diabet*[tiab] AND (“type II"[tiab] OR "type 2”[tiab])) OR T2D[tiab] OR “non insulin*”[tiab] OR noninsulin[tiab] OR non-insulin[tiab])

13.3 HF AND Obesity

("Heart Failure"[Mesh] OR heart failure*[tiab] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR ((heart[tiab] OR cardia*[tiab] OR myocardial[tiab]) AND (failure[tiab] OR insuffienc*[tiab] OR decompensate*[tiab])))
AND
("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "Mineralocorticoid Receptor Antagonists"[Mesh] OR "sacubitril and valsartan sodium hydrate drug combination"[Supplementary Concept] OR gliflozin*[tiab] OR canagliflozin*[tiab] OR dapagliflozin*[tiab] OR empagliflozin*[tiab] OR ertugliflozin*[tiab] OR spironolacton*[tiab] OR eplerenon*[tiab] OR sacubitril*[tiab] OR SGLT[tiab] OR gliflozin*[tiab] OR MRA[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND
("Obesity"[Mesh] OR “Overweight”[Mesh] OR obesity[tiab] OR obese[tiab] OR overweight[tiab])

13.4 HF AND COPD

("Heart Failure"[Mesh] OR heart failure*[tiab] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR ((heart[tiab] OR cardia*[tiab] OR myocardial[tiab]) AND (failure[tiab] OR insuffienc*[tiab] OR decompensate*[tiab])))
AND
("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "Mineralocorticoid Receptor Antagonists"[Mesh] OR "sacubitril and valsartan sodium hydrate drug combination"[Supplementary Concept] OR gliflozin*[tiab] OR canagliflozin*[tiab] OR dapagliflozin*[tiab] OR empagliflozin*[tiab] OR ertugliflozin*[tiab] OR spironolacton*[tiab] OR eplerenon*[tiab] OR sacubitril*[tiab] OR SGLT[tiab] OR gliflozin*[tiab] OR MRA[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND
(“Pulmonary Disease, Chronic Obstructive”[MeSH] OR "Bronchitis, Chronic"[Mesh] OR "Pulmonary Emphysema"[Mesh] OR COPD[tiab] OR COAD[tiab] OR “chronic bronchitis”[tiab] OR emphysema[tiab] OR (chronic[tiab] AND (obstruct*[tiab] OR limit*[tiab])) OR (obstruct*[tiab] AND (airflow*[tiab] OR airway*[tiab] OR respirat*[tiab] OR lung[tiab] OR pulmonary[tiab])))

13.5 HF AND Pulmonary hypertension

("Heart Failure"[Mesh] OR heart failure*[tiab] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR ((heart[tiab] OR cardia*[tiab] OR myocardial[tiab]) AND (failure[tiab] OR insuffienc*[tiab] OR decompensate*[tiab])))
AND
("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "Mineralocorticoid Receptor Antagonists"[Mesh] OR "sacubitril and valsartan sodium hydrate drug combination"[Supplementary Concept] OR gliflozin*[tiab] OR canagliflozin*[tiab] OR dapagliflozin*[tiab] OR empagliflozin*[tiab] OR ertugliflozin*[tiab] OR spironolacton*[tiab] OR eplerenon*[tiab] OR sacubitril*[tiab] OR SGLT[tiab] OR gliflozin*[tiab] OR MRA[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND
("Hypertension, Pulmonary"[Mesh] OR "Pulmonary Heart Disease"[Mesh] OR ((pulmonary[tiab] OR lung[tiab]) AND hypertension[tiab]) OR PAH[tiab])

13.6 HF AND Chronic kidney disease

("Heart Failure"[Mesh] OR heart failure*[tiab] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR ((heart[tiab] OR cardia*[tiab] OR myocardial[tiab]) AND (failure[tiab] OR insuffienc*[tiab] OR decompensate*[tiab])))
AND
("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "Mineralocorticoid Receptor Antagonists"[Mesh] OR "sacubitril and valsartan sodium hydrate drug combination"[Supplementary Concept] OR gliflozin*[tiab] OR canagliflozin*[tiab] OR dapagliflozin*[tiab] OR empagliflozin*[tiab] OR ertugliflozin*[tiab] OR spironolacton*[tiab] OR eplerenon*[tiab] OR sacubitril*[tiab] OR SGLT[tiab] OR gliflozin*[tiab] OR MRA[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND
("Kidney Failure, Chronic"[Mesh] OR “kidney disease”[tiab] OR “renal disease” [tiab] OR “chronic kidney” [tiab] OR “chronic renal” [tiab] OR “kidney failure”[tiab] OR “renal failure”[tiab] OR CKD[tiab] OR CKF[tiab] OR CRF[tiab] OR CRD[tiab] OR nephropath*[tiab])

13.7 HF AND cachexia/sarcopenia

("Heart Failure"[Mesh] OR heart failure*[tiab] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR ((heart[tiab] OR cardia*[tiab] OR myocardial[tiab]) AND (failure[tiab] OR insuffienc*[tiab] OR decompensate*[tiab])))
AND
("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "Mineralocorticoid Receptor Antagonists"[Mesh] OR "sacubitril and valsartan sodium hydrate drug combination"[Supplementary Concept] OR gliflozin*[tiab] OR canagliflozin*[tiab] OR dapagliflozin*[tiab] OR empagliflozin*[tiab] OR ertugliflozin*[tiab] OR spironolacton*[tiab] OR eplerenon*[tiab] OR sacubitril*[tiab] OR SGLT[tiab] OR gliflozin*[tiab] OR MRA[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND
("Cachexia"[Mesh] OR "Sarcopenia"[Mesh] OR cachect*[tiab] OR cachex*[tiab] OR sarcopen*[tiab] OR wasting[tiab])

14 Appendix. Excluded references

References that were excluded after consulting the full text, and reasons for exclusion.

14.1 Diabetes

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