AP-HP. Centre Université de Paris

Université Paris Cité

Nouveautés dans l'insuffisance cardiaque

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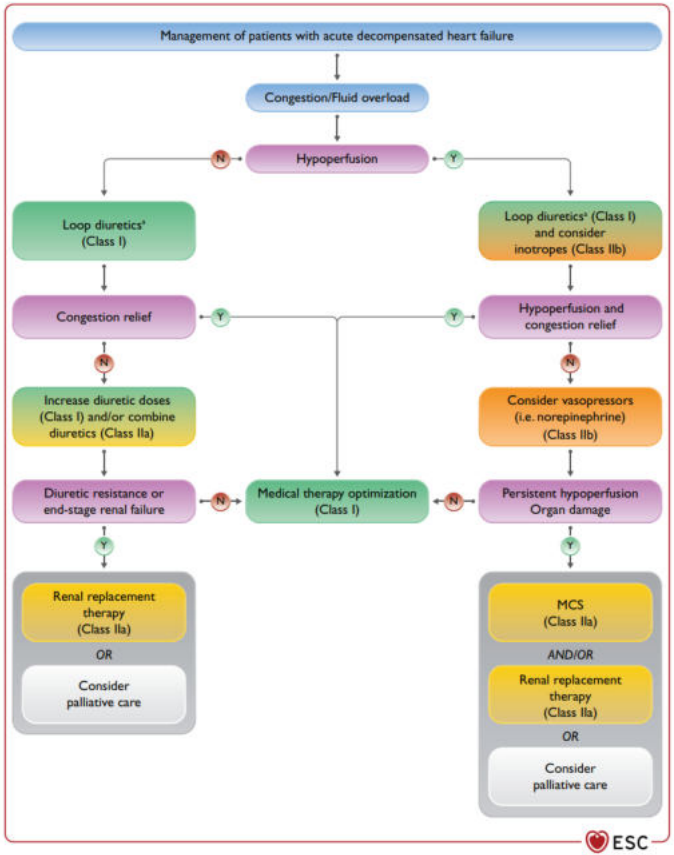
FACT : French Alliance for Cardiovascular clinical Trials

Liens d’intérêts

- **Bourses de recherche :** Abbott, Astra-Zeneca, Bayer
- **Honoraires (orateur ou consultant) :** Abbott, Amarin, Amgen, Astra-Zeneca, Bayer, Bouchara-Recordati, Biotronik, BMS, Boehringer Ingelheim, Bracco, Daiichi-
  Sankyo, Lilly, MSD, Novartis, Novo, Organon, Pfizer, Sanofi, Servier, S unpharm, Vifor Pharma

Insuffisance cardiaque aigue

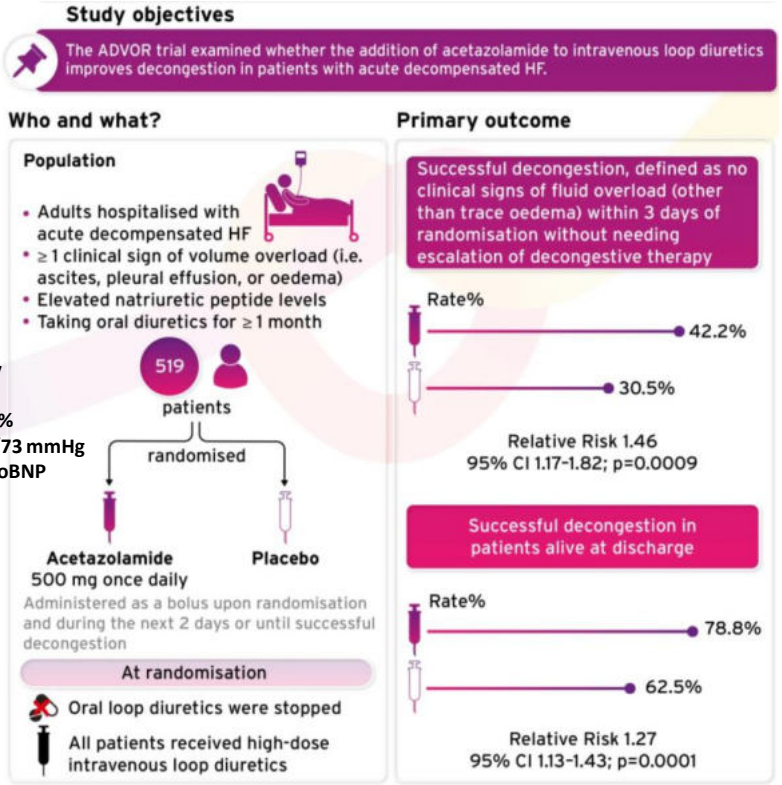
2021 ESC Guidelines for Acute Heart Failure



- **Oxygénation** (saturation >96%)
- **Déplétion par diurétiques** (diurétique de l'anse + diurétiques thiazidique en cas de congestion réfractaire IIB →IIA)
- **Vasodilatateur IV** si PAS >110 mmHg (IIA→IIB)

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

ADVOR : Acetazolamide in AHF



Mean age 78 y
Male 68%
Mean LVEF 43%
Mean PA 127/73 mmHg
Median NT-proBNP 6173 pg/ml

Conclusion

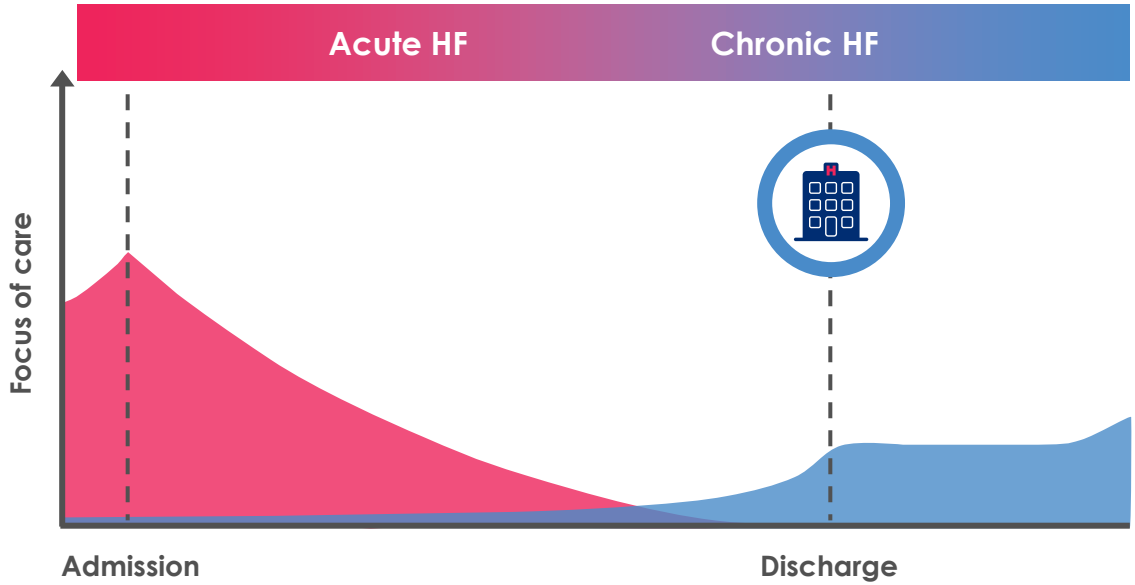
Acetazolamide added to intravenous loop diuretics decreases congestion within 3 days in patients with acute decompensated heart failure

Impact on clinical practice

Acetazolamide is easy to use, safe, effective, off-patent and cheap. It is therefore expected that the results will lead to a paradigm shift in the treatment of acute decompensated heart failure

Mullens W et al. NEJM 2022

Timeline of heart failure: The vulnerable period



Readmission rates after HHF are as high as **30% within 60–90 days**

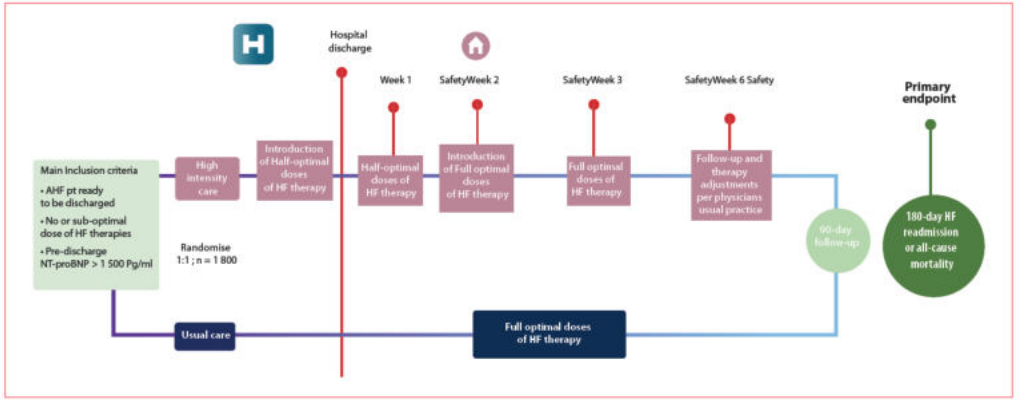
Approximately **10% of patients die within 1 month** of HHF

Figure adapted from Cox ZL et al. Am Heart J 2021
Fonarow GC et al. J Am Coll Cardiol 2007
Bueno H et al. JAMA 2010

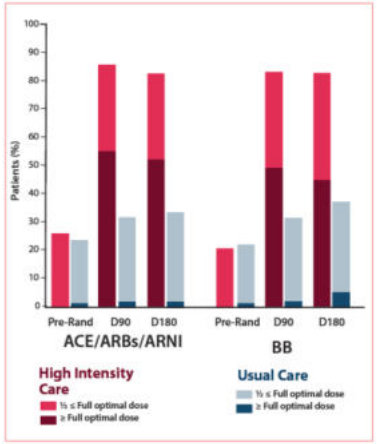
HF, heart failure; HHF, hospitalization for heart failure

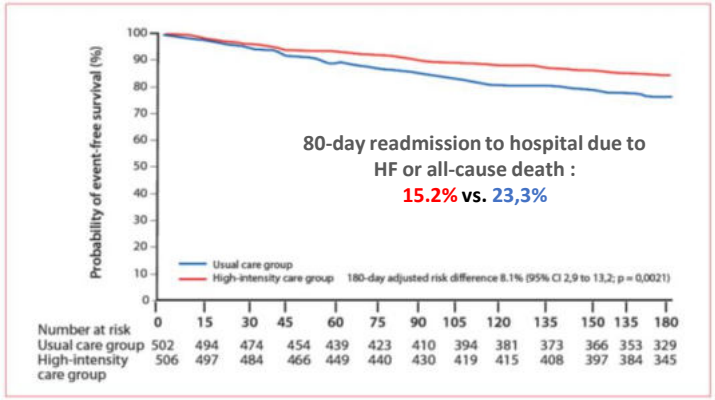
STRONG AF : Rapid Optimization of HF Therapies

1,078 patients with AHF
Multinational, open-label, randomized, parallel-group trial
High-intensity care vs. Usual care
Primary outcome : 80-day readmission to hospital due to HF or all-cause death
Secondary outcomes : Efficacy and safety



Mean age 63y
Male 62%
DM 29%
LVEF ≤ 40% 68%



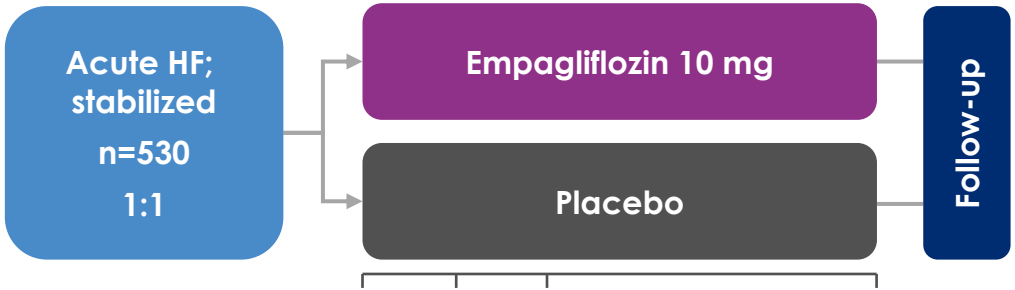


An intensive treatment strategy of rapid up-titration of guideline-directed medication and close follow-up after an AHF admission was readily accepted by patients because it reduced symptoms, improved quality of life, and reduced the risk of 180-day all-cause death or HF readmission compared with

Mebazaa A et al. Lancet 2022

EMPULSE : Empagliflozin in AHF

EMPULSE was specifically designed to prospectively address **in-hospital initiation of empagliflozin** in patients hospitalized for **acute heart failure**, regardless of LVEF or de novo or decompensated chronic presentation



Median time from hospital admission to randomization was **3 days**

Primary endpoint

- **Clinical benefit evaluated with a win ratio based on a composite of:**
  - Death
  - Number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits)
  - Time to first HFE
  - ≥5 point difference in the KCCQ-TSS change from baseline after 90 days of treatment

CV, cardiovascular; HF, heart failure; HFE, heart failure event; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

Tromp J et al. Eur J Heart Fail 2021
Voors AA et al. Nat Med 2022

EMPULSE : Empagliflozin in AHF

All of the following criteria must apply for inclusion

1

Systolic BP ≥100 mmHg and no symptoms of hypotension in the preceding **6 hours**

2

No increase in IV diuretic dose for **6 hours** prior to randomization

3

No IV vasodilators including nitrates within the last **6 hours** prior to randomization

4

No IV inotropic drugs for **24 hours** prior to randomization

BP, blood pressure; IV, intravenous

Tromp J et al. Eur J Heart Fail 2021
Voors AA et al. Nat Med 2022

EMPULSE : Empagliflozin in AHF

Statistical analysis of primary endpoint : The win ratio

Clinical benefit

Each patient from one treatment arm is compared with each patient from the other arm*

$$\text{Win ratio} = \frac{\text{Total number of wins in the empagliflozin group}}{\text{Total number of wins in the placebo group}}$$

1 Death
- Death is worse than no death
- Earlier death is worse

If neither patient is superior based on death

2 Number of HFEs†
- More HFEs is worse

If neither patient is superior based on death or number of HFEs

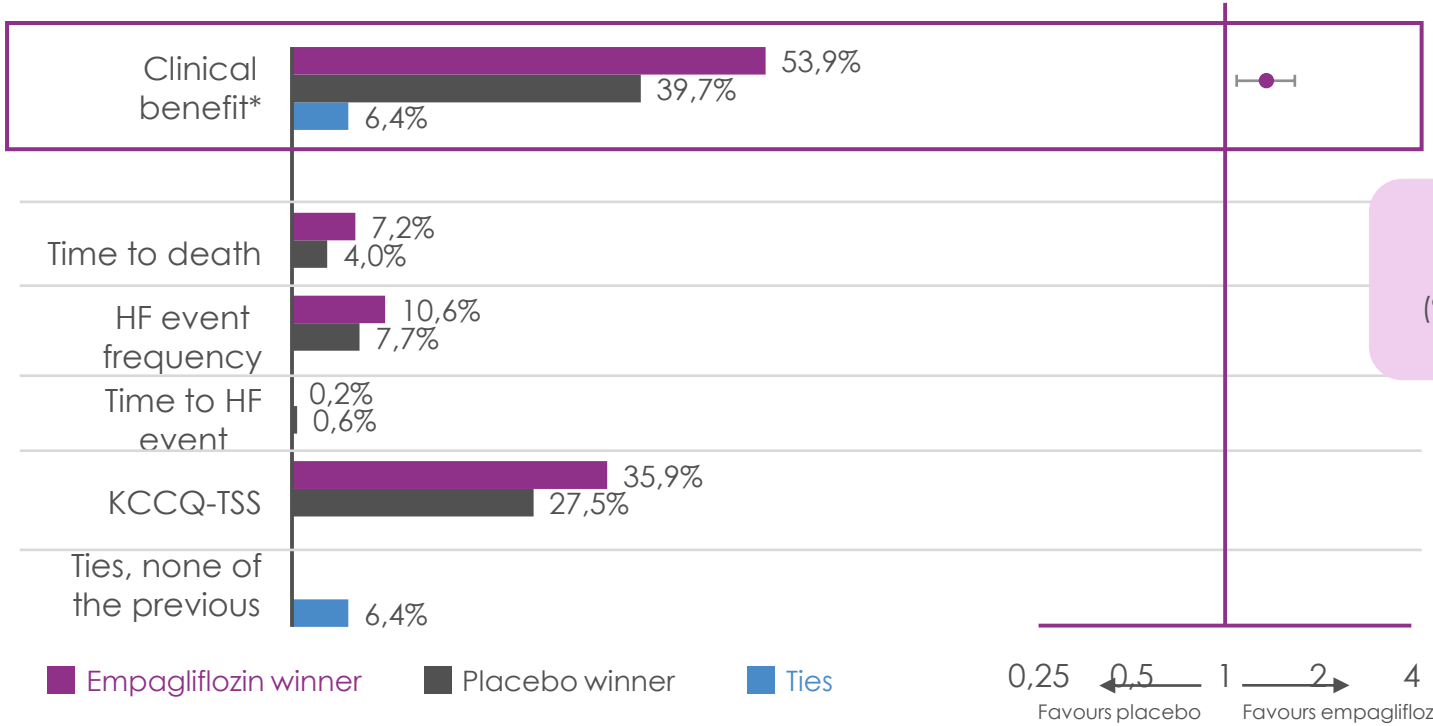
3 Time to first HFE†
- Earlier HFE is worse

If neither patient is superior based on 1–3

4 KCCQ-TSS mean change from baseline after 90 days
- More positive change is better
- Threshold for the difference is ≥5 for a win

* Stratified by HF status (i.e. de novo HF vs decompensated chronic HF). †Within common follow-up time; HFEs include HHF, urgent HF visits and unplanned outpatient visits. HF, heart failure; HFE, heart failure event; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score.

EMPULSE : Empagliflozin in AHF



Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

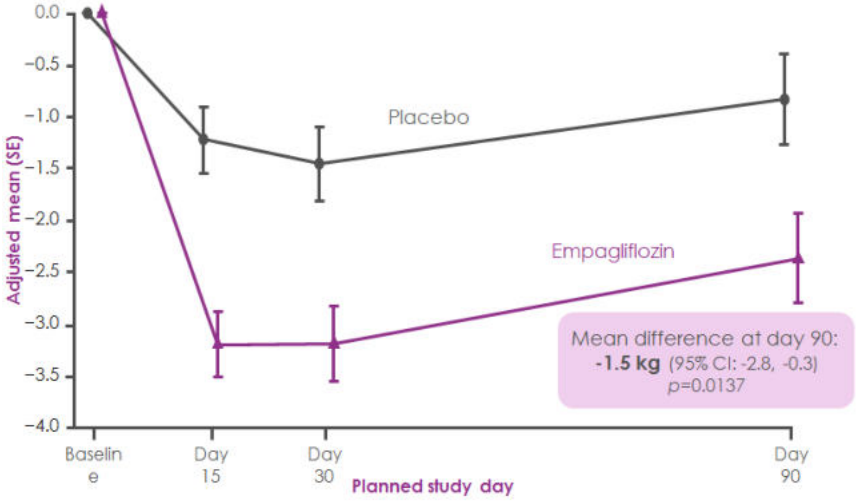
Death:
Empagliflozin: 4.2%
Placebo: 8.3%

HF event:
Empagliflozin: 10.6%
Placebo: 14.7%

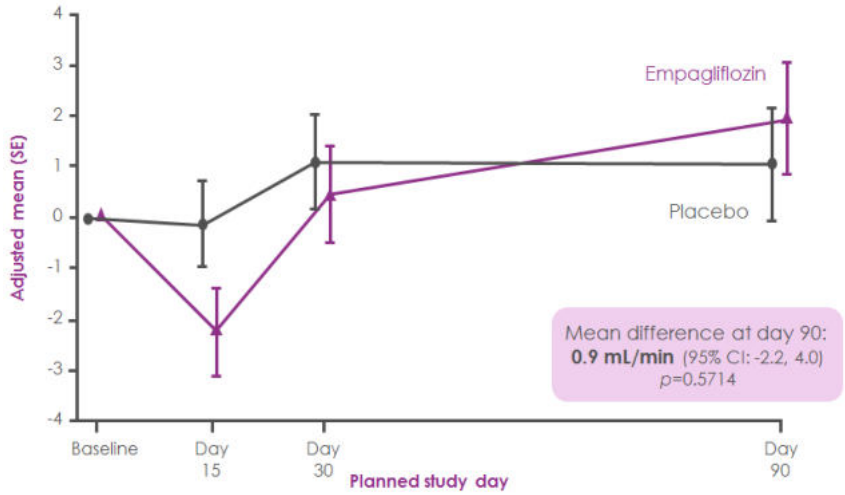
Tromp J et al. Eur J Heart Fail 2021
Voors AA et al. Nat Med 2022

EMPULSE : Empagliflozin in AHF

Secondary endpoints



Body weight change from baseline (kg)



eGFR change from baseline (mL/min)

EMPULSE : Empagliflozin in AHF

Subgroup analysis

	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *p*-value
	Number of patients			
All patients	265	265	1.36 (1.09, 1.68)	
HF status				0.7590
De novo	88	87	1.29 (0.89, 1.89)	
Decompensated chronic	177	178	1.39 (1.07, 1.81)	
Baseline diabetes status				0.5683
Diabetic	124	116	1.47 (1.07, 2.02)	
Non-diabetic	141	149	1.30 (0.97, 1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01, 1.90)	
≥70 years	149	136	1.43 (1.06, 1.92)	
Sex				0.6923
Male	179	172	1.39 (1.06, 1.81)	
Female	86	93	1.27 (0.88. 1.83)	
Region				0.0602
Asia	31	25	0.66 (0.34, 1.30)	
Europe	168	171	1.59 (1.20, 2.09)	
North America	66	69	1.32 (0.87, 2.00)	

EMPULSE : Empagliflozin in AHF

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				0.5683
			1.47 (1.07, 2.02)	
			1.30 (0.97, 1.73)	
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				0.6923
Male	179	172	1.39 (1.06, 1.81)	
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Europe	168	171	1.59 (1.20, 2.09)	
North America	66	69	1.32 (0.87, 2.00)	

The clinical benefits were consistent, regardless of whether patients presented with de novo or decompensated chronic HF

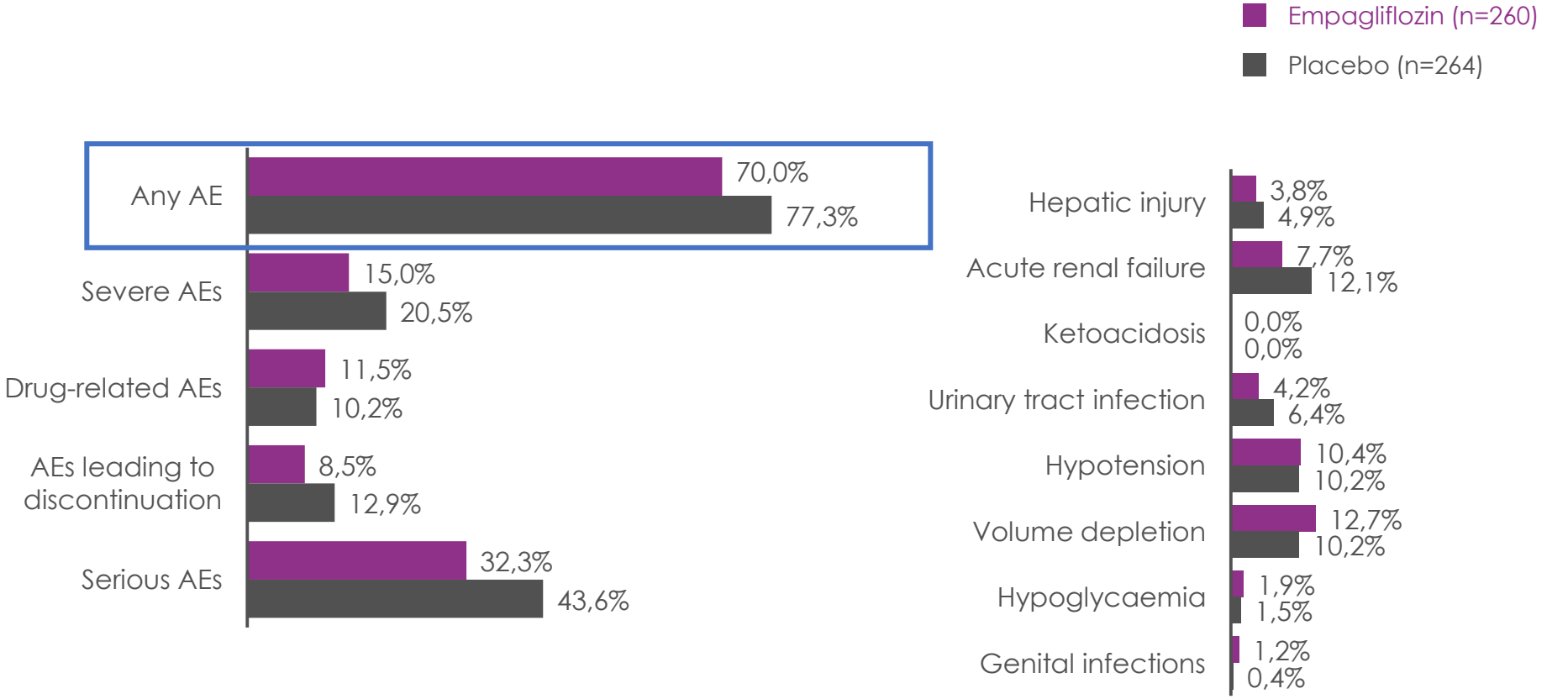
EMPULSE : Empagliflozin in AHF

Subgroup analysis

	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *p*-value
	Number of patients			
All patients	265	265	1.36 (1.09, 1.68)	
NT-proBNP at baseline, pg/mL				0.7904
<Median	125	130	1.36 (0.99, 1.85)	
≥Median	130	126	1.44 (1.06, 1.96)	
eGFR (CKD-EPI) at baseline, mL/min/1.73 m²				0.7562
			1.38 (1.04, 1.83)	
			1.48 (1.04, 2.13)	
				0.1129
			1.68 (1.22, 2.32)	
			1.18 (0.88, 1.59)	
Baseline LVEF, %				0.9008
≤40	182	172	1.35 (1.04, 1.75)	
>40	76	93	1.39 (0.95, 2.03)	

The clinical benefits were independent of LVEF (including patients with HFrEF or HFpEF)

EMPULSE : Empagliflozin in AHF



iSGLT2 and Acute Heart Failure

	DAPA ACT HF-TIMI 68	EMPULSE
Interventions	Dapagliflozin 10 mg daily or placebo (1:1[b])	Empagliflozin 10 mg daily or placebo (1:1[d])
Treatment timing	From ≥24 hrs to Day 7 of admission until 2 months	From within 24 hrs to Day 5 of admission until 90 days
Patient population	• Age ≥18 years • Currently hospitalized for AHF and stabilized • LVEF ≤40% within last 12 months • Elevated NT-proBNP or BNP • With or without T2D • eGFR[c] ≥30 mL/min/1.73 m^2	• Age ≥18 years[e] • Hospitalized for AHF (any LVEF) and stabilized[f] • Dyspnea and ≥2 of the following: congestion on CXR, rales on chest auscultation; clinically relevant edema, or elevated JVP • Elevated NT-proBNP or BNP • With or without T2D • ≥40 mg IV furosemide or equivalent[g] • eGFR ≥20 mL/min/1.73 m^2
Sample size	~2400	530 (actual)
Primary outcome	• Time to first occurrence of CV death or worsening HF	• Clinical benefit at 90 days (hierarchical composite of time to all-cause death, number of HF events,[h] time to first HF event and ≥5-point increase from BL in KCCQ-TSS)
Key secondary outcomes	• Time to first occurrence of composite of CV death, rehospitalization for HF, or urgent HF visit • Time to first occurrence of composite of CV death or rehospitalization for HF • Time to first occurrence of rehospitalization for HF or urgent HF visit • Readmission within 30 days of hospital discharge • Time to CV death • Time to death	• Improvement in KCCQ-TSS of ≥10 points after 90 days • Change from BL in KCCQ-TSS after 90 days • Change from BL in NT-proBNP over 30 days • Days alive and out of hospital until 30 days after initial hospital discharge and 90 days after randomization • Time to first occurrence of CV death or HF event[i] until end-of-trial visit • Occurrence of hHF until 30 days after initial hospital discharge
Completion	February 2023 (estimated)	2021

Insuffisance cardiaque chronique

2021 ESC Guidelines for Chronic Heart Failure

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

Sévérité de l'insuffisance cardiaque :
- Classification NYHA I à IV
- Classification INTERMACS (NYHA III-IV)

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

2021 ESC Guidelines for Chronic Heart Failure

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
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HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

HFrEF & iSGLT2

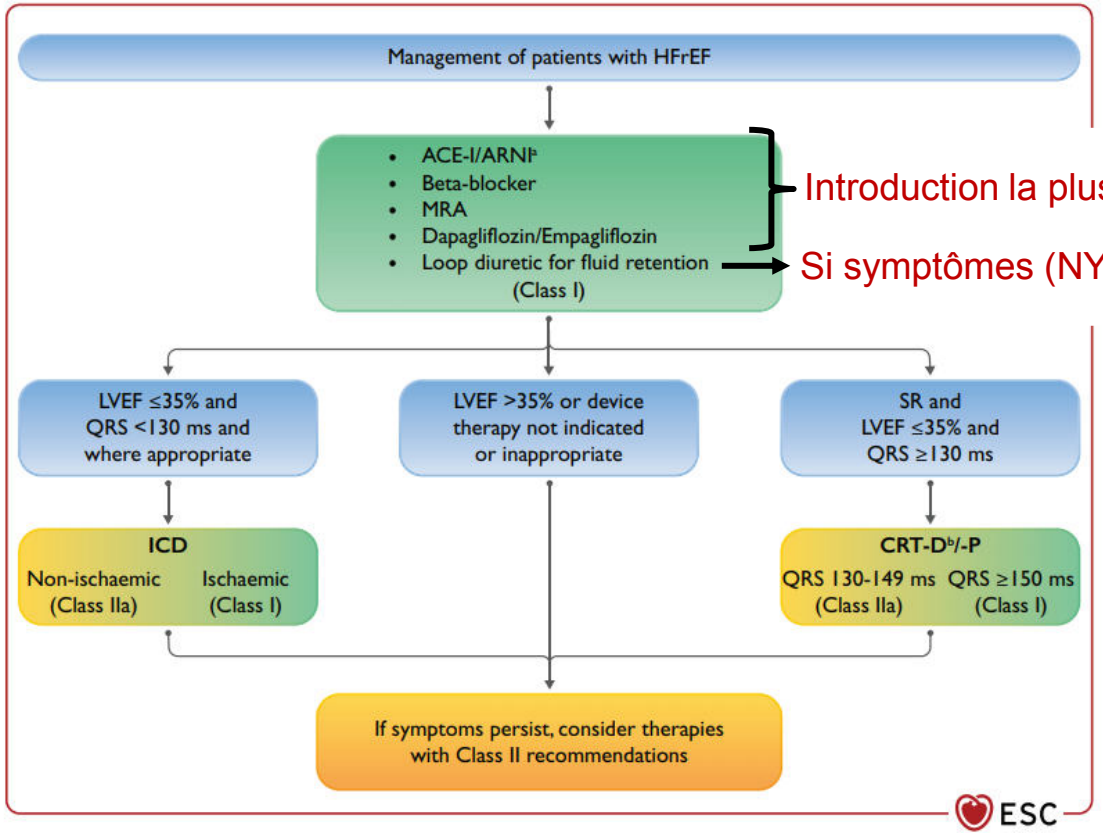
LVEF ≤ 40%

	MACE* HR (95%CI)	HHF HR (95%CI)	CV Death HR (95%CI)
DAPA-HF[1]	**0.71** (0.65-0.85)	**0.70** (0.59-0.83)	**0.82** (0.69-0.98)
EMPEROR-REDUCED[2]	**0.75** (0.65-0.86)	**0.69** (0.59-0.81)	**0.92** (0.75-1.12)

** CV death or HF event (%)*

1. McMurray JJV et al. N Engl J Med 2019
2. Packer M et al. N Engl J Med 2020

Heart Failure with reduced Ejection Fraction (HFrEF)



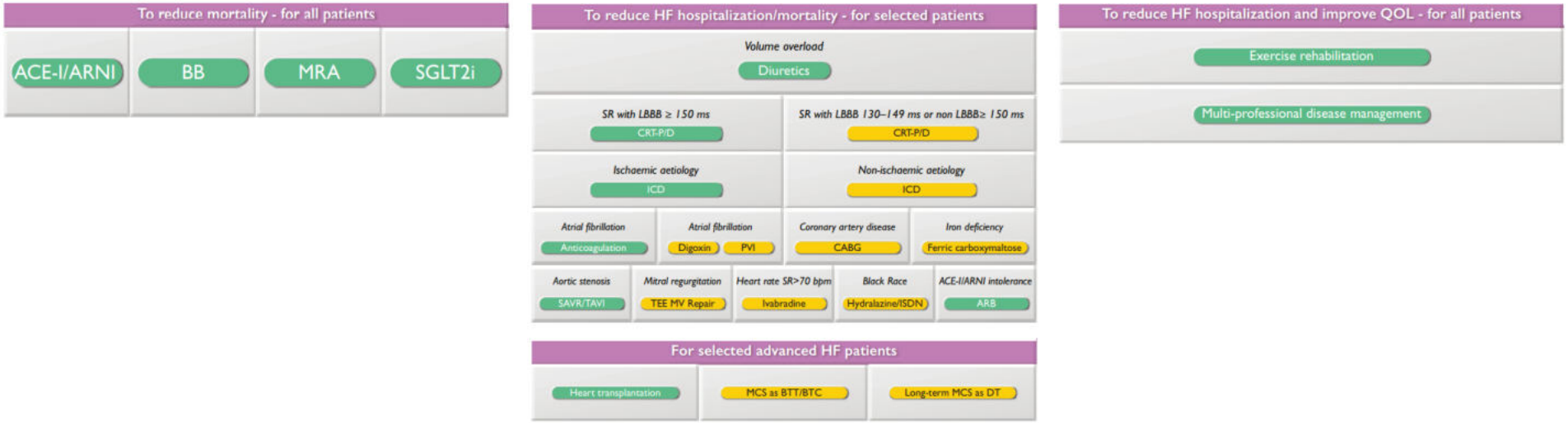
EUROPEAN SOCIETY OF CARDIOLOGY

Introduction la plus précoce possible +++

Si symptômes (NYHA II-IV)

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Heart Failure with reduced Ejection Fraction (HFrEF)



ACE-I= angiotensin-converting enzyme inhibitor; ARB= angiotensin receptor blocker; ARNI= angiotensin receptor-neprilysin inhibitor; BB= beta-blocker; b.p.m.= beats per minute; BTC = bridge to candidacy; BTT= bridge to transplantation; CABG= coronary artery bypass graft; CRT-D= cardiac resynchronization therapy with defibrillator; CRT-P= cardiac resynchronization therapy with pacemaker; DT= destination therapy; HFrEF= heart failure with reduced ejection fraction; ICD= implantable cardioverter-defibrillator; ISDN= isosorbide dinitrate; LBBB= left bundle branch block; MCS= mechanical circulatory support; MRA= mineralocorticoid receptor antagonist; MV= mitral valve; PVI= pulmonary vein isolation; QOL= quality of life; SAVR= surgical aortic valve replacement; SGLT2i= sodium-glucose co-transporter 2 inhibitor; SR= sinus rhythm; TAVI= transcatheter aortic valve replacement; TEE= transcatheter edge to edge

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

2021 ESC Guidelines for Chronic Heart Failure

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Heart Failure with mildly reduced Ejection Fraction (HFmrEF)

- Elle est considérée physiopathologiquement plus proche de l'HFrEF que de l'HFpEF
- **Le seul traitement recommandé de manière formelle est le traitement diurétique à visée symptomatique (I,C)**
- Les traitements piliers de l'HFrEF incluant les IEC/ARA2, bêta-bloquants, anti-aldostérone ou le sacubitril-valsartan sont des classes thérapeutiques pouvant être considérées (IIb,C)

2021 ESC Guidelines for Chronic Heart Failure

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Heart Failure with preserved Ejection Fraction (HFpEF)

- La prise en charge est basée sur le traitement à visée symptomatique, diurétiques (I,C), des comorbidités (I,C) et sur le traitement d'une étiologie sous-jacent si identifiée
- Aucun traitement n’a prouvé son efficacité sur la mortalité
- Le traitement de l’HTA permet de diminuer ou retarder les hospitalisations, et peut être associé aux statines chez les patients à haut risque CV (classe IA). Chez les patients diabétiques, l’utilisation d’iSGLT2 permet de prévenir les hospitalisations pour insuffisance cardiaque.

HFpEF & iSGLT2

LVEF > 40%

	MACE* HR (95%CI)	HHF HR (95%CI)	CV Death HR (95%CI)
DELIVER[1]	**0,82** (0.73-0.92)	**0.79** (0.69-0.91)	**0.88** (0.74-1.05)
EMPEROR-PRESERVED[2]	**0.79** (0.69-0.90)	**0.71** (0.60-0.83)	**0.91** (0.76-1.09)

** CV death or HF event (%)*

1. Solomon SD et al. N Engl J Med 2022
2. Anker J. Butler SD et al. N Engl J Med 2021

FINEARTS-HF: Finerenone in adult patients with HFpEF

Objective

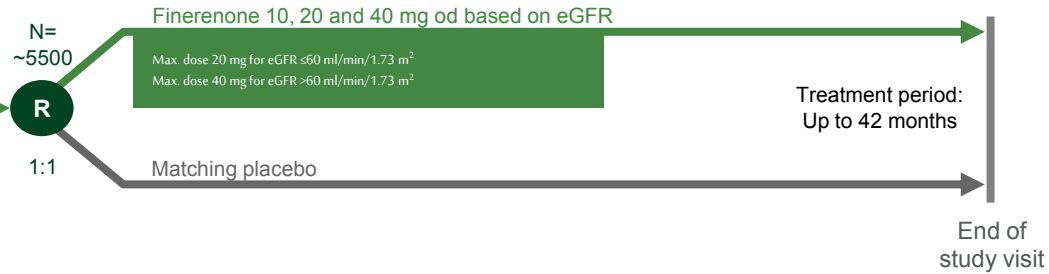
To evaluate the efficacy and safety of finerenone on morbidity and mortality in patients with symptomatic HF (NYHA class II–IV and LVEF ≥40%)

Key inclusion criteria:

- Aged ≥40 years
- HF diagnosis with NYHA class II–IV (ambulatory or hospitalised primarily for HF)
- LVEF ≥40% measured within last 12 months
- Structural heart abnormalities within last 12 months
- NT-proBNP ≥300 pg/ml (BNP ≥100 pg/ml) in patients with sinus rhythm; NT-proBNP ≥900 pg/ml (BNP ≥300 pg/ml) in patients with AF*

Key exclusion criteria:

- eGFR <25 ml/min/1.73 m²
- Serum plasma potassium >5.0 mmol/l
- MI or any event which could have reduced the EF
- Acute inflammatory heart disease, CABG, stroke or TIA within last 90 days or PCI in the last 30 days
- Alternative causes of HF symptoms#
- SBP ≥160 mmHg‡



Design
Multicentre, randomised, double-blind, parallel-group, placebo-controlled phase III study

Primary outcome measures
Number of CV deaths and HF events from baseline to month 42

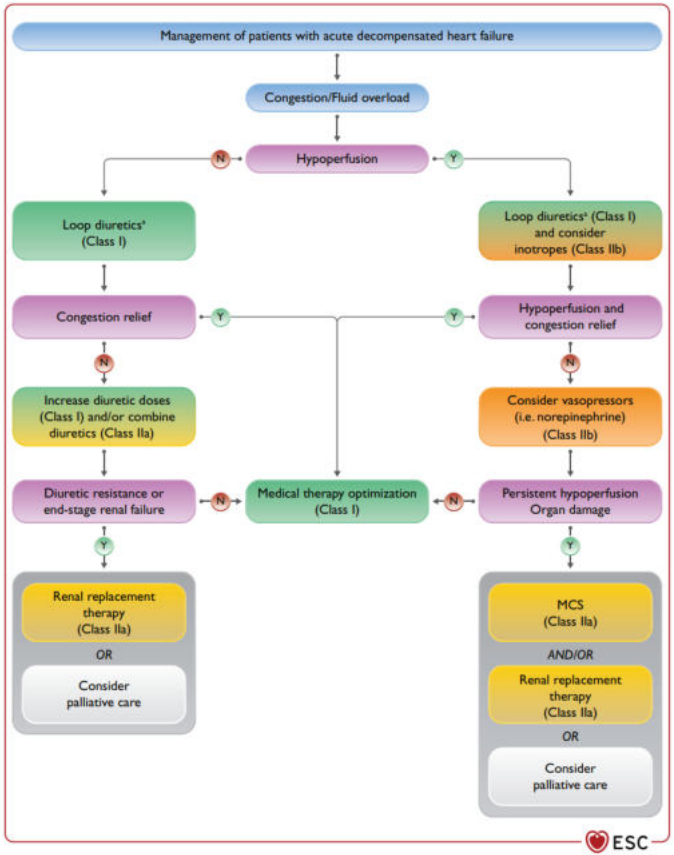
Secondary outcome measures
Measures of QoL; time to first occurrence of composite renal endpoint; time to all-cause death

*Obtained ≤90 days prior to randomisation if HHF requiring initiation or change in HF therapy or urgent visit for HF requiring IV diuretic therapy; or ≤30 days prior to randomisation if no HHF or urgent HF visit within the last 90 days; #Severe pulmonary disease requiring home oxygen, or chronic oral steroid therapy; history of primary pulmonary arterial hypertension, haemoglobin <10 g/dl, valvular heart disease considered by the investigator to be clinically significant, BMI >50 kg/m²; ‡If no treatment with ≥3 BP-lowering medications or SBP ≥180 mmHg irrespective of treatments, on two consecutive measurements ≥2 minutes apart. BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; EF, ejection fraction; IV, intravenous; MI, myocardial infarction; PCI, percutaneous coronary intervention; QoL, quality of life; TIA, transient ischaemic attack

Bayer. https://clinicaltrials.gov/ct2/show/NCT04435626 [accessed 18 June 2020]

FINEARTS-HF

Conclusions



Management of patients with chronic heart failure

HFrEF	HFmrEF	HFpEF
Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%

- ACE-I/ARNI[b]
- Beta-blocker
- MRA
- Dapagliflozin/Empagliflozin
- Loop diuretic for fluid retention

(Class I)

Dapa/Empagliflozin