The golden four in the treatment of heart failure
Heart failure: The basics of clinical cardiology

“Basic task of cardiologist is to know diagnosis and treatment of heart failure”
Sir Thomas Lewis 1913.

“Heart failure is a major health threat of the 21st century, it is frequent, deadly but preventable”
Thomas Luscher, ESC President-elect 2023.
The Heart Failure Association Atlas: Heart Failure Epidemiology and Management Statistics 2019

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Incidence of heart failure per 1000 person-years (left), and prevalence of heart failure per 1000 persons (right)

- **Median annual incidence of HF:** 3.20 per 1000 person-years (IQR 2.66–4.17)
  *Ranging from <2 in Italy, to ≥6 in Estonia and Germany*
- **Median prevalence of HF:** 17.20 per 1000 people (IQR 14.30–21)
  *Ranging from ≤12 in Greece and Spain to >30 in Lithuania and Germany*
Number of HF-related hospital discharges per million people (left) and average length of stay in hospital primarily due to HF (right).

- **Heart failure-related hospital discharge statistics available for 24 countries (57%)**
  - **Median number of HF discharges:** 2671 per million people (IQR 1771–4317)
  - Ranging from <1000 in North Macedonia and United Kingdom to >6000 in Romania, Norway and Germany

- **Days spent in hospital available for 32 countries (76%)**
  - **Median length of stay for hospitalized for HF:** 8.50 days (IQR 7.38–10)
  - Ranging from ≤6 days in Denmark and Poland to ≥11 days in Croatia, Iceland and Belgium

Seferovic P et al. European Journal of Heart Failure (2021)
Hospitals with dedicated HF centers

- Median number of HF centres: **1.16 per million people** (IQR 0.51–2.97)
  *Ranging from <0.50 in Russian Federation, Ukraine, Lebanon, Kyrgyzstan, Romania, Kazakhstan, Azerbaijan, and North Macedonia to >7 in Norway and Italy*

Source: HFA Survey, 2018 or latest year
Data not available: Belgium, Bulgaria, Cyprus, Czech Republic, Poland, Republic of Georgia, Spain, Sweden, Turkey, United Kingdom

Seferovic P et al. European Journal of Heart Failure (2021)
Trilateral Cooperation Project
Starting date: Munich, March 22nd, 2019

Petar M. Seferovic
President of HFA

Randall Starling
President of HFSA

Hiroyuki Tsutsui
President of JHFS
Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association

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Stages in the development and progression of heart failure

AT RISK FOR HEART FAILURE (STAGE A)
- Patients at risk for HF but without current or prior symptoms or signs of HF and without structural, biomarker, or genetic markers of heart disease
- Patients with HTN, CVD, DM, obesity, known exposure to cardiotoxins, family history of cardiomyopathy

PRE-HEART FAILURE (STAGE B)
- Patients without current or prior symptoms or signs of HF but evidence of one of the following:
  - Structural heart disease: e.g., LVH, chamber enlargement, wall motion abnormality, myocardial tissue abnormality, valvular heart disease
  - Abnormal cardiac function: e.g., reduced LV or RV ventricular systolic function, evidence of increased filling pressures or abnormal diastolic dysfunction
  - Elevated natriuretic peptide levels or elevated cardiac troponin levels in the setting of exposure to cardiotoxins

HEART FAILURE (STAGE C)
- Patients with current or prior symptoms and/or signs of HF caused by structural and/or functional cardiac abnormality

ADVANCED HEART FAILURE (STAGE D)
- Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT
- Requiring advanced therapies such as consideration for transplant, mechanical circulatory support, or palliative care

Heart Failure in Remission
- Persistent Heart Failure

with GDMT and risk factor modification

European Journal of Heart Failure (2021)23, 352–380; Journal of Cardiac Failure (2021)27(4) 387-413
Management of HFrEF by phenotype

FOR ALL WITHOUT CONTRAINDICATIONS/INTOLERANCE TO REDUCE MORTALITY
BB
ACEI/ARNI
MRA
SGLT2i

FOR SELECTED SUBGROUPS TO REDUCE HF HOSPITALIZATION/MORTALITY

ARNI/ACEI intolerance
Congestion
Atrial fibrillation
SR, HR > 70 bpm
Iron deficiency
Black race
SR, LBBB ≥150 ms
SR, LBBB ≥150 ms
Ischemic/Not

ARB
Diuretics
Anticoagulation
Ivabradine
Fe-carboximaltose
H-ISDN
CRT-P/D
CRT
CRT-P/D

Digoxine
PVI

SAVR/TAVI
Aortic stenosis
Mitral regurgitation
TEE MV Repair

FOR SELECTED ADVANCED HF TO REDUCE HF HOSPITALIZATION/MORTALITY
Heart transplantation
MCS as BTT/BTC
Long term MCS as DT

FOR ALL TO REDUCE HF HOSPITALIZATION AND IMPROVE QoL
Exercise rehabilitation
Multy-professional disease management

Modified from: 2021 ESC Guidelines for diagnosis and treatment of acute and chronic heart failure. EHJ 2021
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Management of patients with HFrEF

- ACE-I/ARNI
- Beta-blocker
- MRA
- Dapagliflozin/Empagliflozin
- Loop diuretics for fluid retention (Class I)

LVEF ≤35% and QRS <130 ms and where appropriate

ICD
  - Non-ischaemic (Class IIa)
  - Ischaemic (Class I)

If symptoms persist, consider therapies with Class II recommendations

LVEF >35% or device therapy not indicated or inappropriate

CRT-D/V-P
  - QRS 130-149 ms (Class IIa)
  - QRS ≥150 ms (Class I)

MRA

SGLT2i

Diuretics as needed (I)

SR and LVEF ≤35% and QRS ≥130 ms

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Step 1: Establish diagnosis of HFrEF
Step 2: Titrating to target doses as tolerated, labs, and health status
Step 3: Consider these patient scenarios
Step 4: Implement additional GDMT and device therapy, as indicated
Step 5: Reassess symptoms, labs, and LVEF
Step 6: Referral for HF specialty care for additional therapy

EHJ 2021;00:1-128; Circulation. 2022;145:00–00
The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology

Wilfried Mullens, Kevin Damman, Veli-Pekka Harjola, Alexandre Mebazaa, Hans-Peter Brunner-La Rocca, Pieter Martens, Jeffrey M. Testani, W.H. Wilson Tang, Francesco Orso, Patrick Rossignol, Marco Metra, Gerasimos Filippatos, Peter M. Seferovic, Frank Ruschitzka, and Andrew J. Coats
PARADIGM-HF Primary Results

Significant Reduction in Primary Endpoints (CV death or heart failure hospitalization), CV Death and All-Cause Mortality

Switching from ACEi/ARB to sacubitril/valsartan

Benefits of sacubitril/valsartan in “lower than normal” LVEF

Sacubitril/valsartan may be a preferred treatment option compared to either ACEi or ARBs in patients with LVEF <57%

Solon S, McMurray J. Journal of Cardiac Failure Vol. 27 No. 6 2021
HFmrEF/HFpEF (LVEF >40%)
And recent worsening HF event
N=466

Secondary Outcome
Hierarchical composite of a) time to CV death, b) HF hospitalizations, c) urgent HF visits, and d) change in NT-proBNP

- Overall: 36.9% wins with Sac/Val vs. 31.0% with Val
- CV death: 4% Wins with Sac/Val vs. 2.8% with Val
- HF hospitalizations: 13.8% Wins Sac/Val vs. 12.6% with Val
- Urgent HF visits: 2.5% Wins Sac/Val vs. 1.5% with Val
- Change in NT-proBNP: 27.9%
- Ties: 32.1%

Unmatched win ratio = 1.19; 95% CI, 0.93–1.52; P=0.16

Presented by Dr Robert Mentz at Late Breaking Clinical Trials Session, HF Congress 2023, Prague
SGLT2 inhibition
Mechanisms of the cardio-/nephroprotective effects

Primary endpoint: First adjudicated CV death or HF hospitalisation

- HR 0.75
  (95% CI 0.65, 0.86)
  p<0.001

- RRR 25%
- ARR 5.2%
- NNT = 19

Key secondary: Adjudicated total HF hospitalisations (first and recurrent)

- HR 0.70
  (95% CI 0.58, 0.85)
  p<0.001

- RRR 30%

Composite renal endpoint (ESKD or sustained profound decrease in eGFR)

- HR 0.50
  (95% CI 0.32, 0.77)

- RRR 50%
- ARR 1.5%

DAPA-HF: primary composite outcome
CV mortality / HF hospitalisation / Urgent HF visit

HR 0.74 (0.65, 0.85)
p = 0.00001

NNT = 21

26% RRR

DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat.

1. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.
2021 ESC/HFA Guidelines for heart failure
New strategies for medical treatment

- **Quarduple**, instead of triple, basic medical treatment

- **Simultaneous**, instead of sequential, introduction of the drugs

- **Patients profiling** *(Strategic phenotyping)*
Patient profiling in heart failure

STRONG-HF – Study Design

**HF therapy**: combining ACEi/ARB/ARNi & BB & MRA

**Safety**: clinical exam & biology (NT-proBNP, K, Creat, hemoglobin)

**Main inclusion criteria**
- AHF pt ready to be discharged
- No or sub-optimal dose of HF therapies
- Pre-discharge NT-proBNP >1500 pg/ml

**Usual care**

**Randomise 1:1; n = 1800**

**Hospital discharge**

- **Week 1 Safety**: Introduction of Half optimal doses of HF therapy
- **Week 2 Safety**: Half optimal doses of HF therapy
- **Week 3 Safety**: Up-titration to Full optimal doses of HF therapy
- **Week 6 Safety**: Full optimal doses of HF therapy

**Follow-up and therapy adjustments per physicians usual practice**

**Primary endpoint**

180-day HF readmission or all-cause mortality

**90-day follow-up**

**Study terminated 23d Sept 2022 by DSMB (n=1069 pt)**
- larger than expected difference in primary endpoint
- unethical to keep patients in usual care

Mebazaa A et al. The Lancet 2022
STRONG-HF: Primary Endpoint

Primary endpoint:
180-Day Readmission for HF or All-Cause Death

180-Day All-Cause Death

- **High intensity care**
- **Usual care**

180-day risk difference 8.1%
(95% CI 2.9 to 13.2; p=0.0021)

180-day risk difference 1.6%
(95% CI -2.3 to 5.4; p=0.42)

Mebazaa A et al. The Lancet 2022
Article highlight:
Accelerated up-titration and optimized ordering can prevent at least 14 deaths and 47 HF hospitalisations/CV deaths per 1000 treated HFrEF patients over the first 12 months.
2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

PRE-HOSPITAL PHASE
- Timely institution of I.V. diuretics.
- Transfer to ED

ADMISSION PHASE
- Disposition decisions: ICU/CCU, hospital ward, early discharge.

INHOSPITAL AND PRE-DISCHARGE PHASE
- Decongestion
- Early initiation and optimisation of GDMT.

POSTDISHARGE PHASE
- Early follow-up (2 weeks post-discharge)
- GDMT optimisation

COACH
ADVOR
CLOROTIC
EMPULSE
STRONG-HF
Admission phase

COACH trial: intervention vs standard care

Risk-score guided stratification of mortality risk

LOW RISK
Standardised care for 30 days

HIGH RISK
Hospital admission

Clinical judgement

LOW RISK
Usual care for 30 days

HIGH RISK
Hospital admission

12% lower 30-day all-cause or CV mortality / CV hospitalisation

Death from Any Cause or Hospitalization for Cardiovascular Causes (within 30 days)

Adjusted HR, 0.88 (95% CI, 0.78–0.99); P=0.04

5% lower 20-month all-cause or CV mortality / CV hospitalisation

Death from Any Cause or Hospitalization for Cardiovascular Causes (cumulative incidence at 20 mo)

Global disparities in prescription of guideline–recommended drugs for heart failure with reduced ejection fraction

Jasper Tromp and others

European Heart Journal, Volume 43, Issue 23, 14 June 2022, Pages 2224–2234,

Article highlight:
REPORT-HF study: Only ~37% of patients with HFrEF were discharged with at least 3 HF medications. Patients in LMICs were less likely to receive GDMT at target doses.
Management of patients with HFmrEF

- Diuretics for fluid retention (Class I)
- Dapagliflozin/Empagliflozin (Class I)
- ACEI/ARNI/ARB (Class IIb)
- MRA (Class IIb)
- Beta-blocker (Class IIb)
EMPEROR-Preserved: Results

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction

Primary composite endpoint:
Cardiovascular death or heart failure hospitalization

Placebo:
511 patients with event
Rate: 8.7 per 100 patient-years

Empagliflozin:
415 patients with event
Rate: 6.9 per 100 patient-years

HR 0.79 (95% CI 0.69, 0.90)
P = 0.0003

NNT = 31 over 26 months median follow-up
A meta-analysis of clinical trials with patients with CKD (CREDENCE, SCORED, DAPA-CKD, EMPA-Kidney) with and without T2DM demonstrated a favourable impact of SGLT2 inhibition of CKD progression, regardless of T2DM status or the type of CKD.

### Impact of SGLT2 Inhibition on CKD Progression

<table>
<thead>
<tr>
<th>Diagnosis Type</th>
<th>N</th>
<th>Mean baseline eGFR, mL/min per 1.73m²</th>
<th>Events/participants</th>
<th>Event rate per 1000 patient-years</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Diabetic kidney disease or nephropathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CREDENCE</td>
<td>56</td>
<td>215/2202</td>
<td>230/2199</td>
<td>27</td>
<td>0.64 (0.52-0.79)</td>
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<tr>
<td>SCORED</td>
<td>44</td>
<td>375/292</td>
<td>52/292</td>
<td>5</td>
<td>0.71 (0.46-1.08)</td>
</tr>
<tr>
<td>DAPA-CKD</td>
<td>43</td>
<td>93/1271</td>
<td>152/1239</td>
<td>36</td>
<td>0.55 (0.43-0.71)</td>
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<tr>
<td>EMPA-KIDNEY</td>
<td>36</td>
<td>85/1032</td>
<td>133/1025</td>
<td>42</td>
<td>0.56 (0.43-0.74)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>46</td>
<td>368/9797</td>
<td>572/9755</td>
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<td>0.60 (0.53-0.69)</td>
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<tr>
<td><strong>Ischaemic and hypertensive kidney disease</strong></td>
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<tr>
<td>DAPA-CKD</td>
<td>43</td>
<td>18/324</td>
<td>26/363</td>
<td>28</td>
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<td>EMPA-KIDNEY</td>
<td>35</td>
<td>37/706</td>
<td>52/739</td>
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<td>0.69 (0.45-1.05)</td>
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<tr>
<td>Subtotal</td>
<td>38</td>
<td>55/1030</td>
<td>78/1102</td>
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<td>0.70 (0.50-1.00)</td>
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<td><strong>Glomerular disease</strong></td>
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<tr>
<td>DAPA-CKD</td>
<td>43</td>
<td>21/343</td>
<td>46/352</td>
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<td>0.43 (0.26-0.72)</td>
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<td>EMPA-KIDNEY</td>
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<td>69/853</td>
<td>95/816</td>
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<td>0.68 (0.50-0.93)</td>
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<td>Subtotal</td>
<td>42</td>
<td>90/1196</td>
<td>141/1168</td>
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<td>0.60 (0.46-0.78)</td>
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<td><strong>Other kidney disease or unknown</strong></td>
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<tr>
<td>DAPA-CKD</td>
<td>43</td>
<td>10/214</td>
<td>14/198</td>
<td>25</td>
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<td>EMPA-KIDNEY</td>
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<td>36/713</td>
<td>52/725</td>
<td>26</td>
<td>0.72 (0.47-1.10)</td>
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<td>Subtotal</td>
<td>38</td>
<td>46/927</td>
<td>66/933</td>
<td>--</td>
<td>0.74 (0.51-1.08)</td>
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<td><strong>Any diagnosis</strong></td>
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<tr>
<td>CREDENCE</td>
<td>56</td>
<td>153/2202</td>
<td>230/2199</td>
<td>27</td>
<td>0.64 (0.52-0.79)</td>
</tr>
<tr>
<td>SCORED</td>
<td>44</td>
<td>375/292</td>
<td>52/292</td>
<td>5</td>
<td>0.71 (0.46-1.08)</td>
</tr>
<tr>
<td>DAPA-CKD</td>
<td>43</td>
<td>142/2152</td>
<td>243/2152</td>
<td>33</td>
<td>0.56 (0.45-0.68)</td>
</tr>
<tr>
<td>EMPA-KIDNEY</td>
<td>37</td>
<td>227/304</td>
<td>332/305</td>
<td>36</td>
<td>0.64 (0.54-0.76)</td>
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<tr>
<td>Total</td>
<td>44</td>
<td>559/12950</td>
<td>857/12948</td>
<td>--</td>
<td>0.62 (0.56-0.69)</td>
</tr>
</tbody>
</table>

Heterogeneity across groups of primary kidney disease: p=0.67

Trend across trials sorted by eGFR for any diagnosis: p=0.88

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes: FIDELIO-DKD

N=5734 pts with CKD and T2DM, UACR 30 to <300, eGFR 25 to <60 ml/min/1.73 m², and diabetic retinopathy, or UACR 300-5000, eGFR of 25 to <75 ml/min/1.73 m², median FUP, 2.6 years.

In patients with CKD and T2DM, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo.

Design and baseline characteristics of STEP-HFpEF program: semaglutide in patients with obesity HFpEF phenotype

Potential mechanisms of benefit for semaglutide in the obesity phenotype of HFpEF

- ↓Plasma volume
- ↓Visceral and pericardial fat
- ↓Demand on high cardiac output
- ↓Cardiac and pulmonary pressures
STEP-HFpEF: results

N= 529 patients with HFpEF (LVEF ≥45%) and BMI ≥30 kg/m²
Semaglutide vs. placebo for 52 weeks
Dual primary end points: change from baseline in the KCCQ score and change in body weight

1. Change in KCCQ clinical score:
   Estimated difference, 7.8 points, p<0.001

2. Change in body weight:
   Estimated difference, 10.7% points, p<0.001

Treatment with semaglutide resulted in more wins than placebo, with a win ratio of 1.72 (95% CI, 1.37 to 2.15; P<0.001).

The wins favoured semaglutide over placebo for all key components of the hierarchical composite endpoint.
Conventional vs. comprehensive HFrEF medical treatment

Cross-trial analysis EMPHASIS-HF (N=2,737), PARADIGM-HF (N=8,399), and DAPA-HF (N=4,744)

Projected mean time to first hospitalisation for HF or CV death for patients starting at age 55

Conventional therapy 6.4 years (4.8–8.0)
ACEi/ARB+β-blocker

Comprehensive therapy 14.7 years (12.6–17.1)
ARNi+β-blocker+MRA+SGLT2i

Difference +8.3 years (6.2–10.7) — by replacing ACEi/ARB with ARNi and adding MRA+SGLT2i

Values shown include 95% CI.