# OS ESTUDOS DE 2022/23 QUE MUDAM A PRÁTICA NA PERSPETIVA DA MEDICINA INTERNA

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Declaro não apresentar conflitos de interesse que possam ser relacionados com a apresentação.

# DELIVER

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# Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*

**DELIVER trial** - ensaio de fase 3, internacional, multicêntrico, de grupos paralelos, orientado por eventos, duplamente cego, randomizado e controlado.

**N = 6263**

**Aleatorização de 1:1**

- Dapaglifozina 10mg
- Placebo

**CRITÉRIOS DE INCLUSÃO:**

- FEVE > 40% e evidência de doença cardíaca estrutural
- > 40 anos (com ou sem diabetes *mellitus* tipo 2)
- Doentes em ambulatório ou hospitalizados por IC
- NT-pro BNP elevado
- TFG ≥ 25 mL/min/1.73m$^2$

*Follow up* 2,3 anos

***ENDPOINT* PRIMÁRIO**

Agravamento da insuficiência cardíaca

(definido como hospitalização por insuficiência cardíaca ou consulta urgente por insuficiência cardíaca não planeada)

**OU**

Morte cardiovascular.

***Endpoints* secundários:**

- número total de eventos por agravamento da insuficiência cardíaca (IC) e morte cardiovascular
- alteração do *score Kansas City Cardiomyopathy Questionnaire* ao 8º mês
- morte cardiovascular
- morte de qualquer causa

# *ENDPOINT* PRIMÁRIO

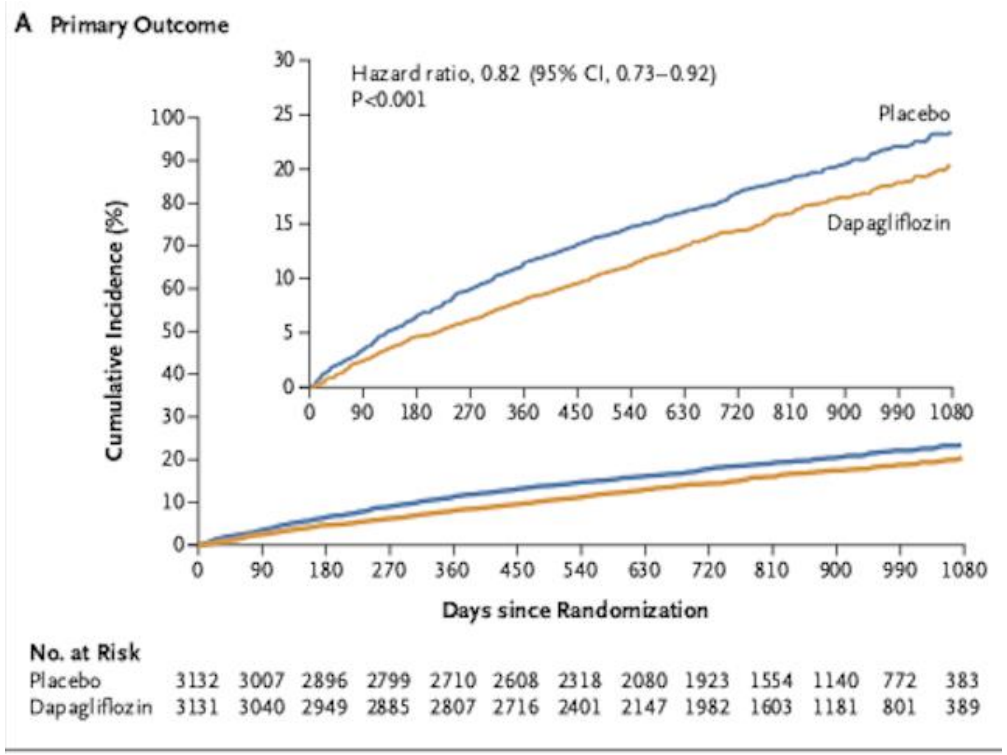



**Table 2.** Primary and Secondary Cardiovascular Outcomes and Safety Outcomes in the Overall Population.*

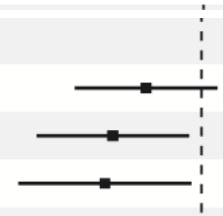
| Variable | Dapagliflozin (N=3131) | | Placebo (N=3132) | | Hazard or Rate Ratio or Win Ratio (95% CI) | P Value |
|---|---|---|---|---|---|---|
| | *values* | *events/ 100 patient-yr* | *values* | *events/ 100 patient-yr* | | |
| **Efficacy outcomes** | | | | | | |
| Primary composite outcome — no. (%) | 512 (16.4) | 7.8 | 610 (19.5) | 9.6 | 0.82 (0.73–0.92) | <0.001 |
| Hospitalization for heart failure or an urgent visit for heart failure | 368 (11.8) | 5.6 | 455 (14.5) | 7.2 | 0.79 (0.69–0.91) | NA |
| Hospitalization for heart failure | 329 (10.5) | 5.0 | 418 (13.3) | 6.5 | 0.77 (0.67–0.89) | NA |
| Urgent visit for heart failure | 60 (1.9) | 0.9 | 78 (2.5) | 1.1 | 0.76 (0.55–1.07) | NA |
| Cardiovascular death† | 231 (7.4) | 3.3 | 261 (8.3) | 3.8 | 0.88 (0.74–1.05) | NA |

# *ENDPOINTS SECUNDÁRIOS*

| | | | | | | |
|---|---|---|---|---|---|---|
| Secondary outcomes | | | | | | |
| Total no. of worsening heart failure events and cardiovascular deaths‡ | 815 | 11.8 | 1057 | 15.3 | 0.77 (0.67–0.89) | <0.001 |
| Change in KCCQ total symptom score at mo 8§ | — | — | — | — | 1.11 (1.03–1.21) | 0.009 |
| Mean change in KCCQ total symptom score at mo 8 among survivors | — | — | — | — | 2.4 (1.5–3.4) | NA |
| Death from any cause — no. (%) | 497 (15.9) | 7.2 | 526 (16.8) | 7.6 | 0.94 (0.83–1.07) | NA |

Although the EMPEROR-Preserved trial suggested some potential attenuation of benefit in the highest part of the range of ejection fraction, we observed no evidence of heterogeneity with respect to left ventricular ejection fraction in the DELIVER trial, with similar overall treatment effects among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%. This finding suggests that the benefit of SGLT2 inhibition is likely to extend throughout the full range of ejection fraction.

| Subgroup | Dapagliflozin | Placebo | Hazard Ratio (95% CI) |
|---|---|---|---|
| | *no. of patients with events/total no.* | | |
| LVEF at enrollment | | | |
| ≤49% | 207/1067 | 229/1049 | 0.87 (0.72–1.04) |
| 50–59% | 174/1133 | 211/1123 | 0.79 (0.65–0.97) |
| ≥60% | 131/931 | 170/960 | 0.78 (0.62–0.98) |



ESC
European Society
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ESC GUIDELINES

# 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

**Recommendation Table 1 — Recommendation for the treatment of patients with symptomatic heart failure with mildly reduced ejection fraction**

| Recommendation | Class[a] | Level[b] |
|---|---|---|
| An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8] | I | A |



CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; SGLT2, sodium–glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.
[c]This recommendation is based on the reduction of the primary composite endpoint used in the EMPEROR-Preserved and DELIVER trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

**Recommendation Table 2 — Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction**

| Recommendation | Class[a] | Level[b] |
|---|---|---|
| An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8] | I | A |

# EMPULSE

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# The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

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**EMPULSE** - double-blind trial, **530 patients** with a **primary diagnosis of acute de novo or decompensated chronic heart failure regardless of left ventricular ejection fraction** were randomly assigned to receive empagliflozin 10 mg once daily or placebo. Patients were randomized in-hospital when clinically stable (median time from hospital admission to randomization, **3 days**) and were treated for **up to 90 days**. The **primary outcome** of the trial was **clinical benefit, defined as a hierarchical composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days, as assessed using a win ratio.**

Evaluate the effects of empagliflozin on **three fundamental goals of care** in patients hospitalized for acute heart failure:

- **improvement of survival;**
- **reduction of heart failure events (HFEs);**
- **improvement of symptoms.**

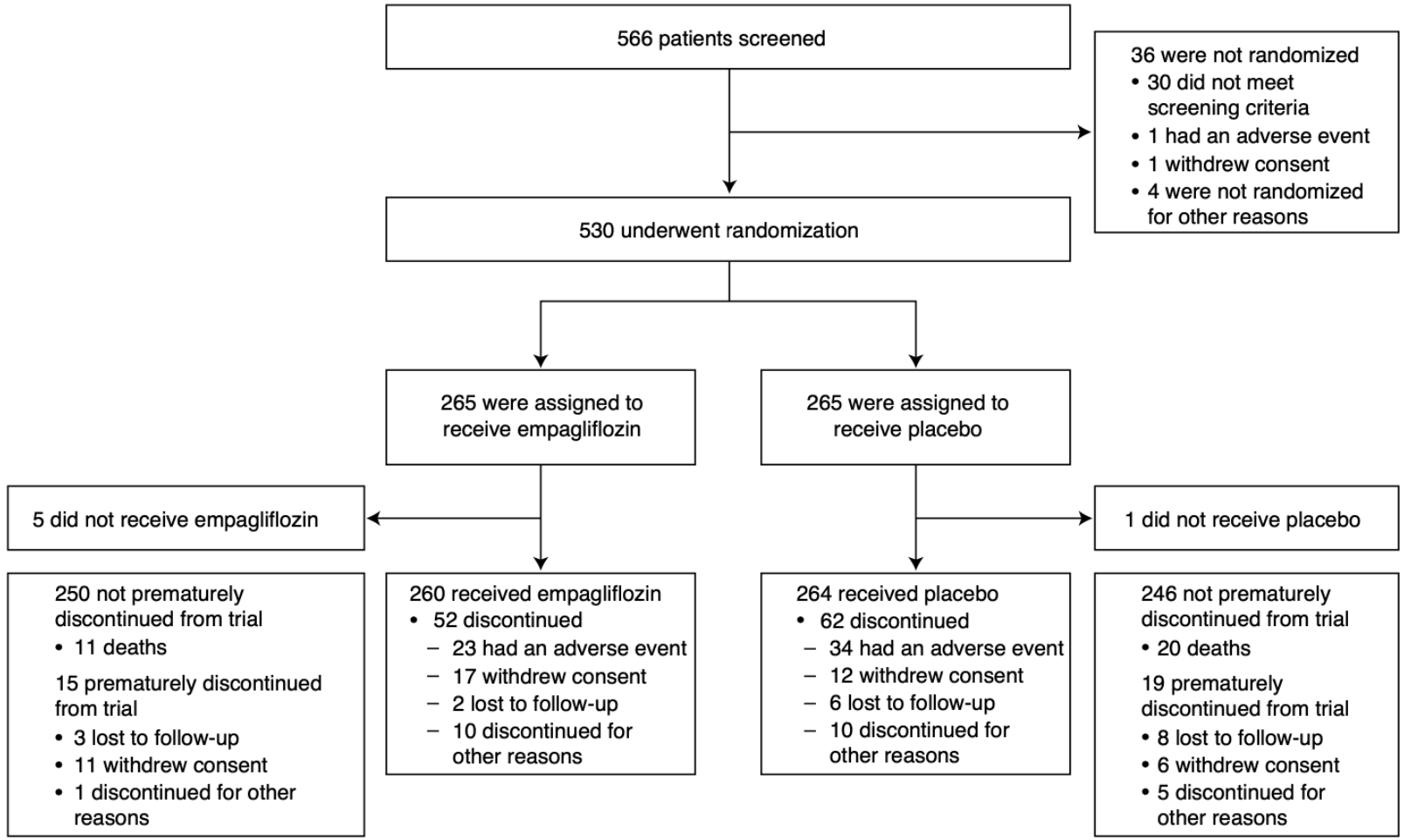


**Fig. 1 | Screening, randomization, and follow-up.** Flowchart of the double-blind EMPULSE trial (NCT04157751), in which 530 patients with a primary diagnosis of acute de novo or decompensated chronic heart failure, regardless of left ventricular ejection fraction, were randomly assigned to receive empagliflozin 10 mg once daily or placebo. This study was carried out at 118 centers in 15 countries.

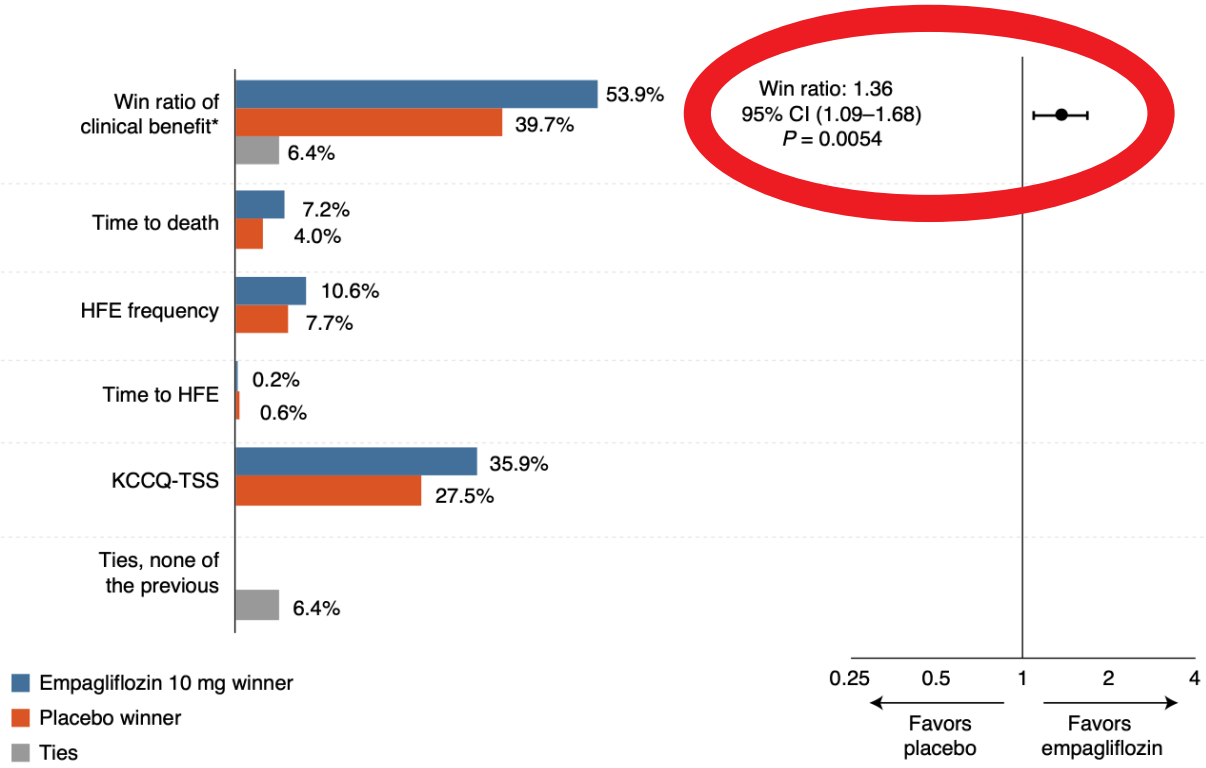


**Fig. 2 | Primary efficacy outcome and components.** The stratified win ratio was calculated using a non-parametric generalized pairwise comparison within heart failure status strata; data are presented as the point estimate and 95% CI with a two-sided *P* value. For the components of the win ratio, the percentages do not reflect randomized comparisons. Please refer to Table 2 for the overall number of events and KCCQ-TSS data. *Hierarchical composite of death, number of HFEs, time to first HFE and change from baseline in KCCQ-TSS after 90 days of treatment.

Primary efficacy analysis of the hierarchical assessment of all-cause mortality, number and time to first HFEs, and change in KCCQ-TSS using the stratified win ratio. **Empagliflozin was superior in 53.9% of paired comparisons and placebo was superior in 39.7%, whereas 6.4% of comparisons were tied, yielding a win ratio of 1.36 in favor of empagliflozin (95% CI: 1.09–1.68, P = 0.0054).**

| Subgroup | Empagliflozin | Placebo | Win ratio (95% CI) | Interaction *P* value |
|---|---|---|---|---|
| | Number of patients | | | |
| All patients | 265 | 265 | 1.36 (1.09–1.68) | |
| Heart failure 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) | |
| Baseline NT-proBNP (pg $ml^{-1}$) | | | | 0.7904 |
| <Median | 125 | 130 | 1.36 (0.99–1.85) | |
| ≥Median | 130 | 126 | 1.44 (1.06–1.96) | |
| Baseline eGFR (CKD-EPI) | | | | 0.7562 |
| ≥60 ml $min^{-1}$ 1.73 $m^{-2}$ | 88 | 106 | 1.48 (1.04–2.13) | |
| <60 ml $min^{-1}$ 1.73 $m^{-2}$ | 161 | 145 | 1.38 (1.04–1.83) | |
| Atrial fibrillation or flutter at baseline | | | | 0.1129 |
| No | 123 | 133 | 1.68 (1.22–2.32) | |
| Yes | 142 | 132 | 1.18 (0.88–1.59) | |
| Baseline LVEF (%) | | | | 0.9008 |
| HFrEF (LVEF ≤40%) | 182 | 172 | 1.35 (1.04–1.75) | |
| HFpEF (LVEF >40%) | 76 | 93 | 1.39 (0.95–2.03) | |

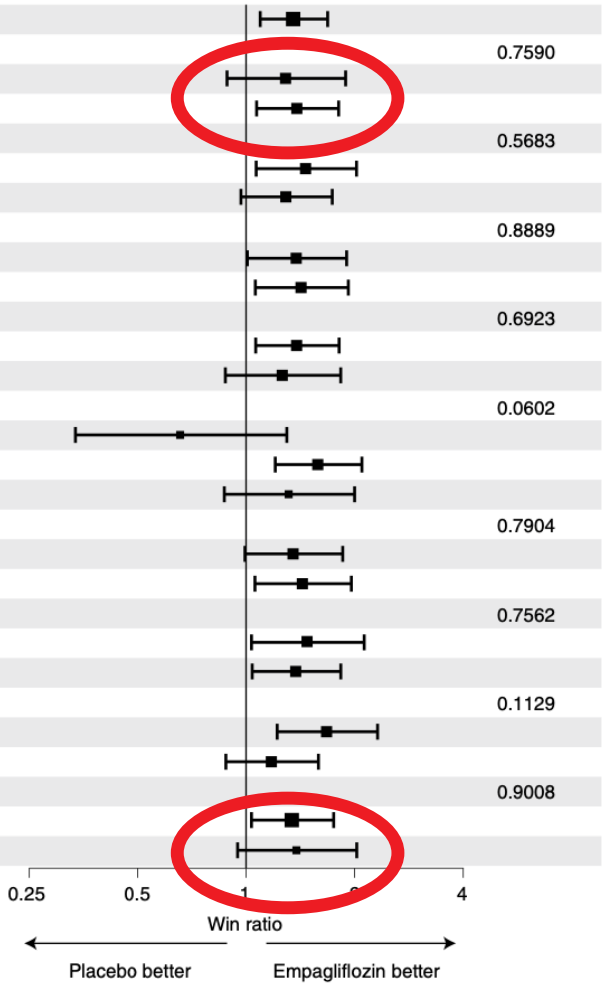


**Fig. 3 | Primary efficacy outcome in all prespecified subgroups.** Win ratios were calculated using a non-parametric generalized pairwise comparison within subgroup strata; data are presented as point estimates and 95% CIs with two-sided interaction *P* values. No adjustments for multiple testing were made. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

**Clinical benefit** was observed for **both acute de novo and decompensated chronic heart failure** and was observed **regardless of ejection fraction** or the presence or absence of diabetes.

These findings indicate that **initiation of empagliflozin in patients hospitalized for acute heart failure is well tolerated** and **results in significant clinical benefit in the 90 days after starting treatment**.

The results of EMPULSE add to the accumulating evidence on the benefits of SGLT2 inhibitors in heart failure. EMPULSE is distinct from previous trials with SGLT2 inhibitors for several reasons. In particular, **patients in EMPULSE were randomized early in the course of hospitalization for acute heart failure**, at a median of 3 days after hospital admission.

Initiation of the SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure **resulted in a statistically significant and clinically meaningful benefit in the 90days after randomization**. Both a **reduction in all-cause death and HFEs as well as an improvement in quality of life** contributed to the increased number of wins in the empagliflozin group. We believe that the **primary endpoint is meaningful** because it allows the hierarchical assessment of **benefit across three fundamental goals of care: improvement of survival, reduction of HFEs, and improvement of symptoms.**

**CONCLUSION:** initiation of empagliflozin as part of usual care in patients who are hospitalized for acute heart failure will result in a clinically meaningful benefit in 90 days without safety concerns.

# DIAMOND

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## Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial

**Javed Butler [1,2]*†, Stefan D. Anker[3,4,5,6]*†, Lars H. Lund [7,8], Andrew J.S. Coats[9], Gerasimos Filippatos [10,11], Tariq Jamal Siddiqi[1,2], Tim Friede [12,13,14], Vincent Fabien [15], Mikhail Kosiborod[16,17], Marco Metra [18], Ileana L. Piña[19], Fausto Pinto[20], Patrick Rossignol [21,22], Peter van der Meer[23], Cecilia Bahit[24], Jan Belohlavek[25], Michael Böhm [26], Jasper J. Brugts[27], John G.F. Cleland[28], Justin Ezekowitz[29], Antoni Bayes-Genis [30], Israel Gotsman[31], Assen Goudev[32], Irakli Khintibidze[33], Joann Lindenfeld[34], Robert J. Mentz[35], Bela Merkely[36], Eliodoro Castro Montes[37], Wilfried Mullens[38], Jose C. Nicolau[39,40], Aleksandr Parkhomenko[41], Piotr Ponikowski[42], Petar M. Seferovic[43,44], Michele Senni[45], Evgeny Shlyakhto[46], Alain Cohen-Solal [47], Peter Szecsödy[15], Klaus Jensen[15], Fabio Dorigotti [15], Matthew R. Weir[48], and Bertram Pitt [49]**

The **DIAMOND** (Patiromer for the Management of Hyperkalemia in Participants Receiving RAASi Medications for the Treatment of Heart Failure) trial was designed to assess the **longer-term ability** of **patiromer** to **control serum potassium**, **prevent hyperkalemia events**, and **improve outcomes and the proportion of patients achieving guideline-recommended doses of RAASi** in patients with HFrEF with hyperkalemia related to RAASi use or a history thereof.

The **DIAMOND trial** was a prospective Phase 3, multicenter, double-blind, randomized withdrawal, placebo-controlled study done at 389 sites in the USA, South America, Europe, and Russia.

**Patiromer** is a novel **potassium-binder** that **exchanges potassium for calcium in the gastrointestinal tract** that can be used to improve control of serum potassium.

**Eligible participants:**

- men or women, aged ≥18 years;
- New York Heart Association (NYHA) Class II–IV heart failure;
- left ventricular ejection fraction ≤40%.

**The protocol required patients to have:**

- hyperkalemia at screening (defined as two serum potassium values of >5.0 mmol/l) while receiving an angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), angiotensin receptor-neprilysin inhibitor (ARNi), and/or MRA therapy;
- normokalemic at screening but had a history of dose reduction or discontinuation of the RAASi therapy due to hyperkalemia in the previous 12 months.

Patients were **excluded** if they had an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m2, systolic blood pressure <90 mmHg or symptomatic hypotension, or any significant comorbidity that could change their clinical course independent of heart failure.

Eligible patients were enrolled into a single-blind run-in phase with weekly visits. Following the run-in phase, eligible patients underwent double-blind randomization in a 1:1 ratio, using a secure, central, interactive, web-based response system to receive continued patiromer or switch to placebo (patiromer withdrawal).

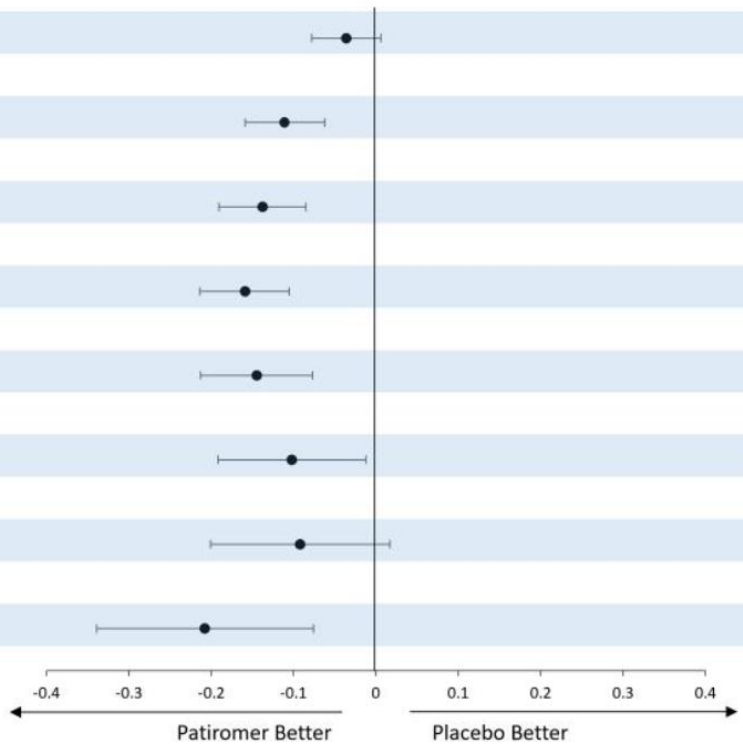
**PRIMARY OUTCOME:**
Adjusted mean change in serum potassium from baseline

The median (interquartile range) duration of follow-up was 27 (13– 43) weeks. The median number of serum potassium assessments for each participant was 5. The **adjusted mean change in serum potassium** from randomization to study end was +0.03 mmol/l (95% CI –0.01, 0.07) in the patiromer group and +0.13 mmol/l (95% CI 0.09, 0.16) in the placebo group, for a between-group difference of – 0.10 mmol/l (95% CI –0.13, –0.07; ***P* < 0.001**). The results of the primary endpoint were consistent in pre-specified subgroups; however, a **significantly greater change from baseline** in serum potassium was reported for participants with **eGFR <45 ml/ min/1.73 m2** [mean change (95% CI) −0.19 (−0.26, −0.12)] compared to participants with eGFR ≥45 ml/min/1.73m2 [mean change (95% CI) −0.08 (−0.11, −0.04)], *P* = 0.003.

**Figure 1** Effects of patiromer vs. placebo on adjusted mean change in serum potassium level (mEq/L) from the baseline to the end of the study period (*A*) difference in adjusted mean change from baseline by visit, and (*B*) mean change from baseline over time. CI, confidence interval.

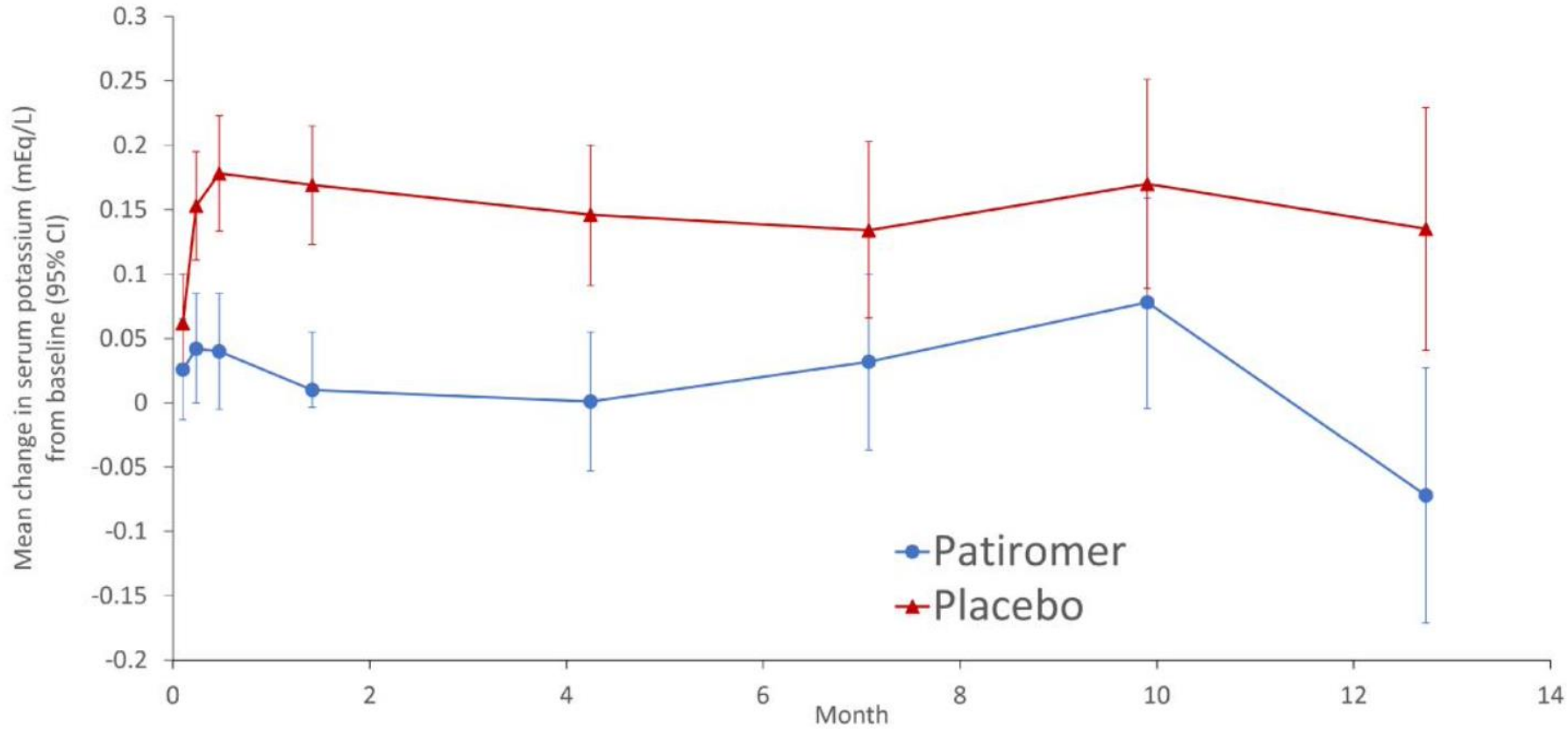
**A**

| Visit | Adjusted mean change in serum potassium level (mEq/L) from baseline (95% CI) | | Difference in adjusted mean change from baseline (95% CI) | p value |
|---|---|---|---|---|
| | Patiromer (N=439) | Placebo (N=439) | | |
| Day 3 | 0.026 (-0.013; 0.065) | 0.062 (0.024; 0.100) | -0.036 (-0.078; 0.006) | 0.089 |
| Week 1 | 0.042 (0.000; 0.085) | 0.153 (0.111; 0.195) | -0.111 (-0.159; -0.062) | **<0.001** |
| Week 2 | 0.040 (-0.005; 0.085) | 0.178 (0.133; 0.223) | -0.138 (-0.191; -0.085) | **<0.001** |
| Week 6 | 0.010 (-0.036 0.055) | 0.169 (0.123; 0.215) | -0.159 (-0.214; -0.105) | **<0.001** |
| Week 18 | 0.001 (-0.053; 0.055) | 0.146 (0.092; 0.201) | -0.145 (-0.213; -0.077) | **<0.001** |
| Week 30 | 0.032 (-0.037; 0.100) | 0.134 (0.065; 0.202) | -0.102 (-0.192; -0.012) | **0.026** |
| Week 42 | 0.078 (-.004; 0.159) | 0.170 (0.089; 0.251) | -0.092 (-0.201; 0.017) | **0.097** |
| Week 54 | -0.072 (-0.171; 0.027) | 0.135 (0.041; 0.229) | -0.208 (-0.339; -0.076) | **0.002** |




CI: confidence interval

**B**




| n | Day 3 | Week 1 | Week 2 | Week 6 | Week 18 | Week 30 | Week 42 | Week 54 |
|---|---|---|---|---|---|---|---|---|
| Patiromer (N=439) | 409 | 406 | 402 | 376 | 273 | 183 | 104 | 66 |
| Placebo (N=439) | 416 | 409 | 397 | 361 | 270 | 184 | 106 | 74 |

# SECONDARY OUTCOMES:

| Variable | Patiromer ($n = 439$) | | Placebo ($n = 439$) | | Outcome (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| | | Events/ 100 py | | Events/ 100 py | | |
| **Secondary outcomes specified in hierarchical testing procedure—*n* (%)** | | | | | | |
| Number of patients with hyperkalemia events [serum potassium >5.5 (mmol/l)] *n* (%) | 61 (13.9) | – | 85 (19·4) | – | Hazard ratio 0.63 (0.45, 0.87) | 0.006 |
| Number of subjects with MRA reduction, *n* (%) | 61 (13.9) | – | 83 (18.9) | – | Hazard ratio 0.62 (0.45, 0.87) | 0.006 |
| Total number of hyperkalemia events | 225 | 77.7 | 316 | 118.2 | Hazard ratio 0.66 (0.53, 0.81) | <0.001 |
| Hyperkalemia- related outcomes win ratio | – | | – | | 1.53 (1.23, 1.91) | <0.001 |
| RAASi use score win ratio[a] | – | – | – | – | 1.25 (1.003, 1.564) | 0.048 |

[a]Win ratio of novel RAASi use score (range 0–8) based on the sequence of all-cause mortality, cardiovascular hospitalization, and one or two points each for the use of ≥50% or ≥100% of target doses of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor, MRA, and beta-blocker.
MRA, mineralocorticoid receptor antagonist; py, person-years; RAASi, renin–angiotensin–aldosterone system inhibitor.

**Key Question**

To investigate the impact of patiromer on serum potassium level and its ability to enable specified target doses of renin-angiotensin-aldosterone inhibitors (RAASi) in patients with heart failure and a reduced ejection fraction (HFrEF).

**Key Finding**

Patiromer significantly reduced serum $K^+$ versus placebo; treatment also reduced mineralocorticoid receptor antagonist (MRA) discontinuation or dose reductions, the number of hyperkalemia events and the win-ratio for hyperkalemia-related morbidity adjusted outcomes versus placebo.

**Take Home Message**

Patiromer use simultaneously reduces the risk of recurrent hyperkalemia and enables specified target doses of RAASi.

# Patiromer use in patients with heart failure and reduced ejection fraction (HFrEF) with hyperkalemia (HK)

## Study design

1195

Patients with HFrEF and hyperkalemia or a history of hyperkalemia

878

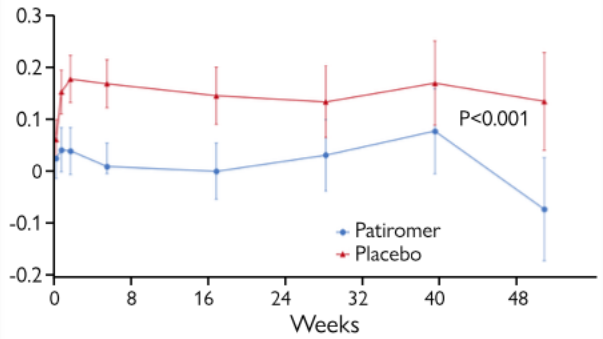
Patients were randomized and completed run-in (where $K^+$ levels controlled with patiromer and RAASi dose optimized)

439 Placebo

439 Patiromer

## Primary endpoint

Mean change in serum potassium (mmol/L) from baseline (95% confidence interval (CI))




| | Day | Weeks | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 | 1 | 2 | 6 | 18 | 30 | 42 | 54 |
| Patiromer | 409 | 406 | 402 | 376 | 273 | 183 | 104 | 66 |
| Placebo | 416 | 409 | 397 | 361 | 270 | 184 | 106 | 74 |

## Secondary endpoints

| | Patiromer (n=439) | Placebo (n=439) | Hazard/rate ratio (95% CI) | P-value |
|---|---|---|---|---|
| Hyperkalemia events with serum $K^+$ > 5.5 mmol/L | 61 (13.9) | 85 (19.4) | 0.63 (0.45-0.87) | 0.006 |
| Maintained MRA target dose | 61 (13.9) | 83 (18.9) | 0.62 (0.45-0.87) | 0.006 |
| Total number of hyperkalemia events | 225 | 316 | 0.66 (0.53-0.81) | <0.001 |

0.3 1 3.0
RR or HR* (95% CI)
**Favours Patiromer** Favours Placebo

| | Win ratio (95% CI) | P-value |
|---|---|---|
| Hyperkalemia-related morbidity-adjusted events* | 1.53 (1.23-1.91) | <0.001 |
| Win-ratio for RAASi use score | 1.25 (1.003-1.564) | 0.048 |

0.3 1 3.0
Win ratio (95% CI)
Favours Placebo **Favours Patiromer**

*Morbidity-adjusted hyperkalemia-related outcomes were tested in a hierarchical manner with the following sequence: cardiovascular death, cardiovascular hospitalization, total hyperkalemia events >6.5 mmol/L, >6.0–6.5 mmol/L, and >5.0–6.0 mmol/L

# PRIORITIZE-HF

ESC HEART FAILURE
*ESC Heart Failure* 2023; **10**: 1066–1076
Published online 23 December 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14268

ORIGINAL ARTICLE

## Potassium reduction with sodium zirconium cyclosilicate in patients with heart failure

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PRIORITIZE-HF was an international, multicentre, parallel-group, randomized, double-blind, placebo-controlled Phase 2 study to evaluate the benefits and risks of using SZC to intensify RAAS inhibitor therapy in patients with heart failure under-treated with an ACEi, ARB or ARNI, and MRA, without inducing clinically significant hyperkalaemia.

Sodium zirconium cyclosilicate (SZC) is an orally administered non-absorbed intestinal potassium binder proven to lower serum potassium concentrations. SZC exchanges potassium for sodium and hydrogen in the intestinal lumen. As SZC is an efficacious treatment of hyperkalaemia, it may facilitate treatment with RAAS inhibitors in patients unable to receive these agents (or where there is concern about pre- scribing them) and allow dose optimization.

At baseline, patients were required to have mild hyperkalaemia or be at risk of developing hyperkalaemia during the study defined as follows:

- estimated glomerular filtration rate (eGFR) 20 to 44 mL/min/1.73 m2 [calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation] and serum potassium concentration between 4.0 and 5.5 mmol/L
- eGFR 45 to 59 mL/min/ 1.73 m2 and serum potassium between 5.1 and 5.5 mmol/L
- eGFR 45 to 59 mL/min/1.73 m2 and serum potassium concentration between 4.0 and 5.0 mmol/L

+

Prior documented serum potassium concentration higher than 5.0 mmol/L attributed to use of a RAAS inhibitor.

Patients with symptomatic HFrEF were eligible and randomly assigned to receive SZC 5 g or placebo once daily for 12 weeks. Doses of study medication and RAAS inhibitors were titrated during the treatment period. The primary endpoint was the proportion of patients at 12 weeks in the following categories:

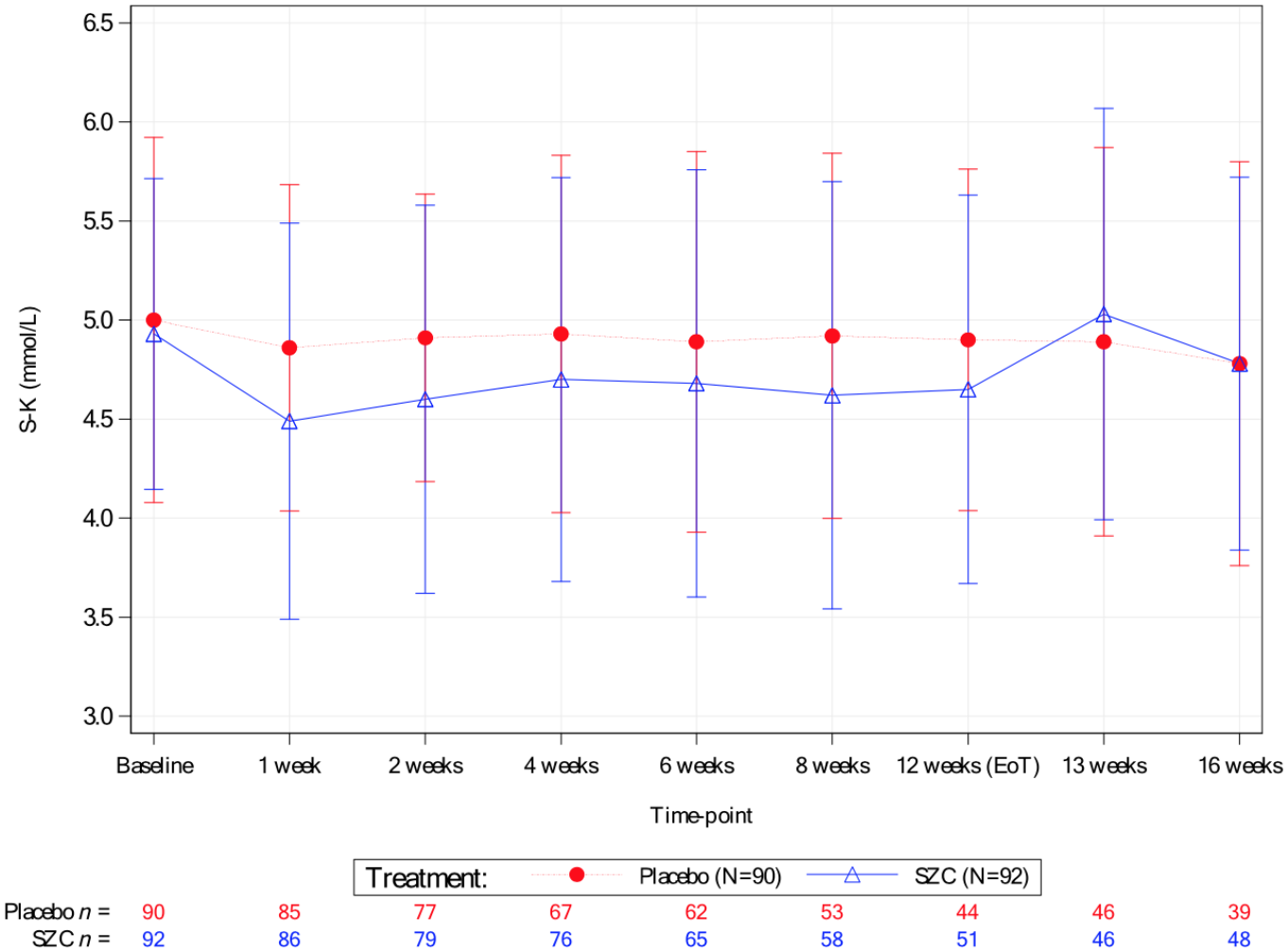
(i) any RAAS inhibitor at less than target dose, and no MRA;
(ii) any RAAS inhibitor at target dose and no MRA;
(iii) MRA at less than target dose;
(iv) MRA at target dose.

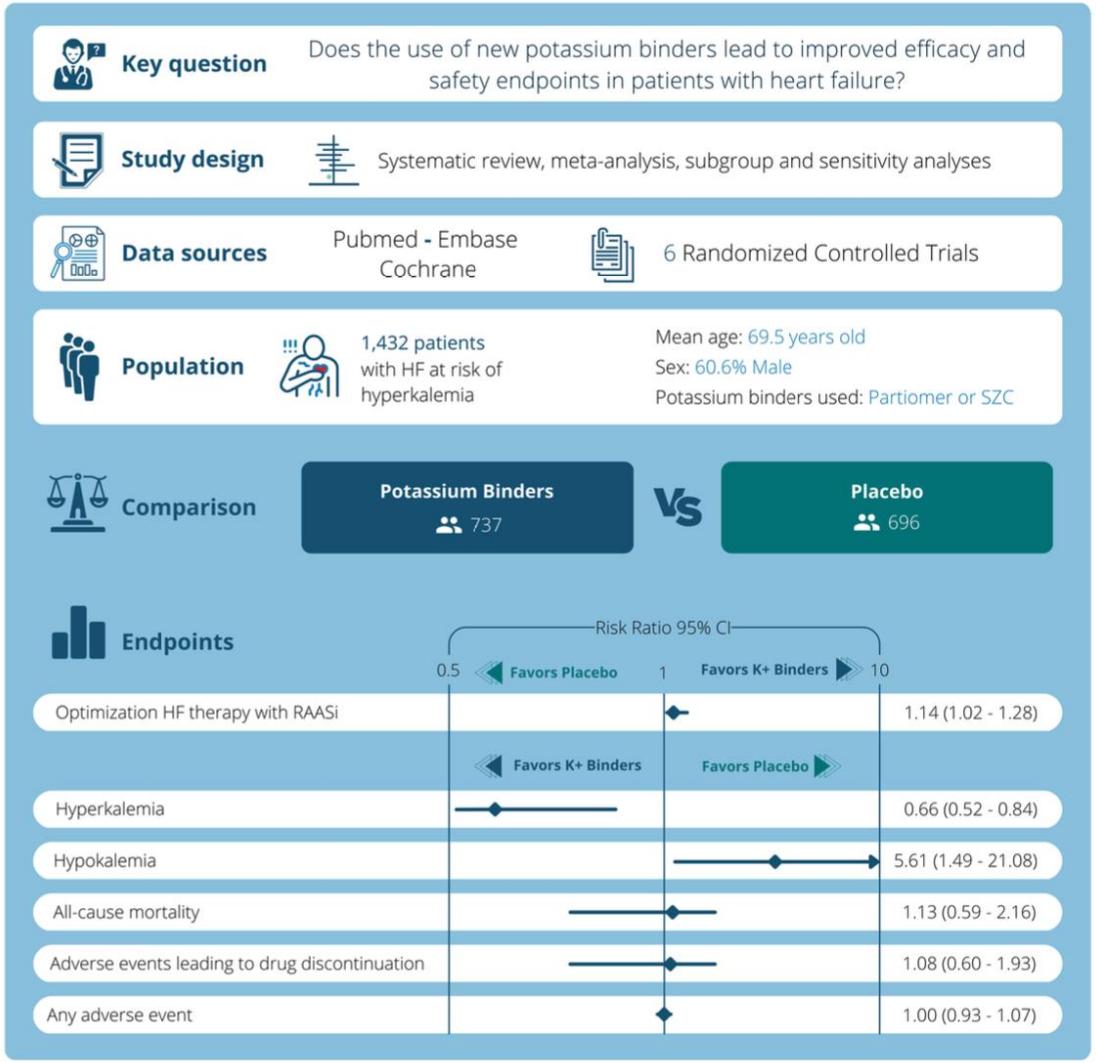
Due to challenges in participant management related to the COVID-19 pandemic, the study was prematurely terminated with 182 randomized patients. There was no statistically significant difference in the distribution of patients by RAAS inhibitor treatment categories at 3 months (P = 0.43).

The proportion of patients at target MRA dose was numerically higher in the SZC group (56.4%) compared with the placebo group (47.0%).

Overall, SZC was well tolerated.

**Figure 1** Mean serum potassium concentrations over time (intent-to-treat population).






# Safety and efficacy of new potassium binders on hyperkalemia management in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials

Pedro E. P. Carvalho[1] · Thiago M. A. Veiga[1] · Henrique Lacerda[1] · Matheus R. Tofanelli[1] · Douglas M. Gewehr[2] · Maria C. P. Nunes[3] · Ana C. Simões e Silva[4]

Received: 27 January 2023 / Accepted: 19 April 2023 / Published online: 4 May 2023


## Conclusion

In this meta-analysis of RCTs including patients with HF at risk of hyperkalemia, the use of new potassium binders, Patiromer and SZC, increased the rates of medical therapy optimization and reduced the risk of hyperkalemia, at the cost of an increased prevalence of hypokalemia. Our results may be useful for the clinical care of patients with HF at risk of hyperkalemia development.

ESC HEART FAILURE
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Published online 24 June 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13976

ORIGINAL ARTICLE

# Experience with the potassium binder patiromer in hyperkalaemia management in heart failure patients in real life

Alberto Esteban-Fernández[1,2]*, Carolina Ortiz Cortés[3], Silvia López-Fernández[4,5], Alejandro Recio Mayoral[6], Francisco Javier Camacho Jurado[7], Inés Gómez Otero[8], María Molina[1,2], Luis Almenar Bonet[9,10] and Raquel López-Vilella[9,10]

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A retrospective multicentre register included all outpatients with HF and HK (K ≥ 5.1 mEq/L) treated with patiromer according to current recommendations.

**Figure 1** Evolution of potassium levels during the follow-up. a = K before patiromer treatment vs. K at 7 days ($P < 0.05$). b = K before patiromer treatment vs. K at 90 days ($P < 0.05$).

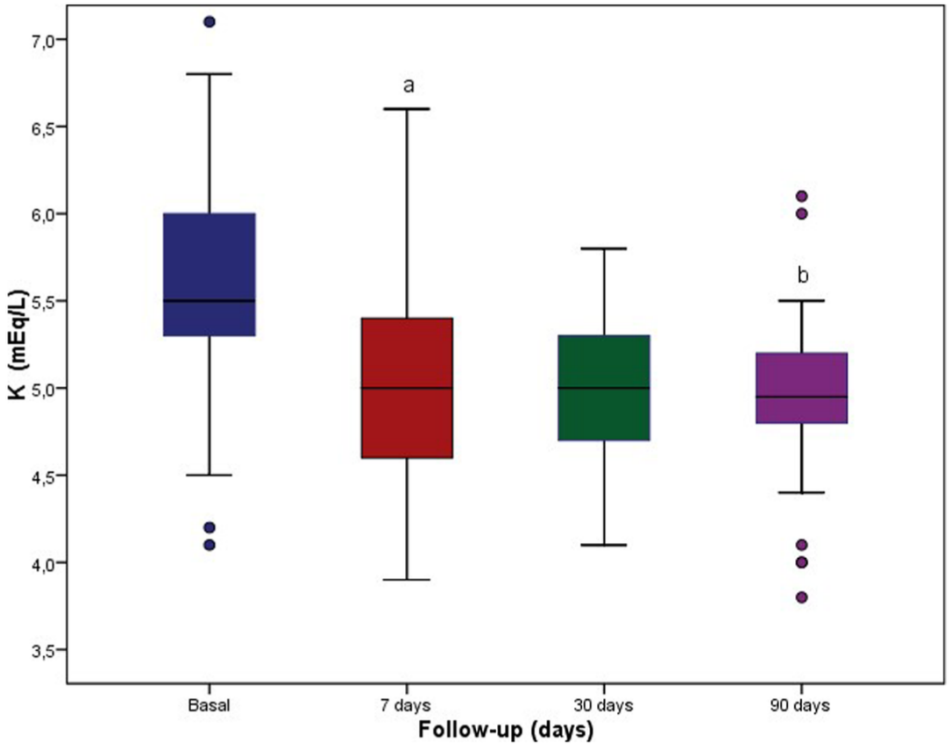
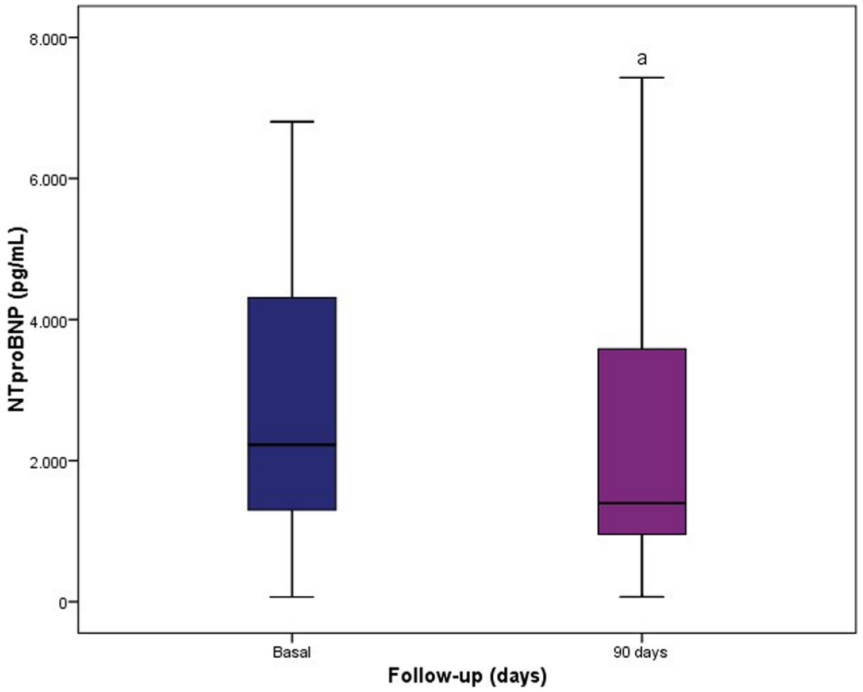


**Figure 2** Evolution of NTproBNP levels during the follow-up. a = NTproBNP before patiromer treatment vs. NTproBNP at 90 days ($P < 0.05$).




## CONCLUSION:

In a real-life cohort of patients with heart failure, patiromer reduced and maintained K levels during 3 months of follow-up. The most common adverse events were hypomagnesaemia and gastrointestinal disturbances. Patiromer helps optimize medical treatment, increasing the percentage of patients treated with RAASi and MRA at target doses. At the end of follow-up, natriuretic peptides values and hospital visits were reduced, suggesting the benefit of optimizing HF medical treatment.

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Editorial

# Pragmatic diagnostic and therapeutic algorithms to optimize new potassium binder use in cardiorenal disease

The latest ESC HF guidelines state that “administration of the K lowering agents, patiromer or sodium zirconium cyclosilicate, may allow renin-angiotensin-aldosterone system (RAAS) inhibitor initiation or uptitration in a larger proportion of patients”

A major hurdle to implementation of potassium-binders is understanding how to integrate them safely and effectively into long-term management protocols for cardiovascular and renal disease.

To address these challenges, a multidisciplinary academic panel including nephrologists and cardiologists was convened to develop a consensus therapeutic algorithm aimed at optimizing the use of two novel potassium binders (Patiromer and SZC) in stable adults who require treatment with RAASi and experience(d) hyperkalaemia.

Providing the clinical community with pragmatic algorithms may help optimize the management of high-risk patients by avoiding the risks of both hypo- and hyperkalaemia and suboptimal RAASi therapy.

**Table 1**
Diagnostic and therapeutic algorithm with patiromer in stable adults with chronic hyperkalaemia ± requirement for RAASi *(Patiromer should not replace emergency treatment for acute life-threatening hyperkalaemia)*.

| Serum K+ (mmol/L) (confirmed by two consecutive valid samples) | | Action* | Additional actions, if clinically required:* | *Individualise recommended actions according to the clinical situation<br>Monitoring† |
|---|---|---|---|---|
| Severe hyperkalaemia | ≥ 6.0 | • Initiate[a,b] patiromer at 8.4 g once daily, or<br>• Up-titrate[b,c] patiromer if started at ≥ 7-day intervals by 8.4 g once daily, to a maximum dose of 25.2 g daily, until serum K+ <5.1 mmol/L | • Suspend RAASi and re-assess serum K+ levels after 3–7 days[d]<br>• Maintain RAASi if started, but re-assess serum K+ levels after 3–7 days:[d]<br>– If K+ levels are still high and patiromer is on maximum dose, consider RAASi down-titration[d]<br>– If K+ levels < 5.1 mmol/L, consider up-titration of RAASi if not on guideline-recommended target dose[d] | • After initiating or changing patiromer dose, measure serum K+ and creatinine within 3–7 days† and repeat after 1 week. If target K+ value is achieved, measure serum K+ at 1 month, then every 3 months<br>• Monitor serum Mg for at least 1 month after initiating patiromer.[f] Consider Mg supplementation in patients who develop low serum Mg levels (0.58 mmol/L)<br>• Any time that a change in electrolyte or volume status is suspected, eg due to gastrointestinal problems, re-measure serum K+ and creatinine and repeat the above monitoring sequence as per standard clinical practice and applicable guideline recommendations<br>†Monitoring frequency should be individualised based on the clinical situation. Some clinical scenarios may require a change in the frequency of monitoring; refer to applicable guidelines for recommendations. |
| Moderate hyperkalaemia | 5.6–5.9 | | | |
| Mild hyperkalaemia | 5.1–5.5 | • Consider initiation[a] of patiromer at 8.4 g once daily, or<br>• Maintain / up-titrate[c] patiromer if started at ≥ 7-day intervals by 8.4 g once daily, to a maximum dose of 25.2 g daily, until serum K+ <5.1 mmol/L | • Initiate / maintain RAASi at guideline-recommended target dose and re-assess serum K+ levels after 7 days[d]<br>• Consider up-titration of RAASi to guideline-recommended target dose[d] depending on the clinical situation and if patiromer has been started[a] | |
| Normokalaemia | 4.1–5.0 | • If started on patiromer, maintain dose | • Initiate / maintain / up-titrate RAASi to guideline-recommended target dose and re-assess serum K+ levels after 7 days[d] | |
| Mild hypokalaemia | 3.5–4.0 | • Stop patiromer[e] if on lowest dose, or<br>• Down-titrate[c] patiromer at ≥ 7-day intervals by 8.4 g once daily | | |
| Hypokalaemia | < 3.5 | • If on patiromer, stop treatment[b,e] | | |

**Table 2**
Diagnostic and therapeutic algorithm with sodium zirconium cyclosilicate in stable adults with chronic hyperkalaemia ± requirement for RAASi *(SZC should not replace emergency treatment for acute life-threatening hyperkalaemia)*.

| Serum K+ (mmol/L) (confirmed by two consecutive valid samples) | | Action* | Additional actions, if clinically required: * | *Individualise recommended actions according to the clinical situation Monitoring† |
|---|---|---|---|---|
| Severe hyperkalaemia | ≥ 6.0 | • Initiate[a,b] SZC at 10 g thrice daily for 24, 48 or 72 h (i.e. until normokalaemia), then proceed to the maintenance phase, starting with 5 g/day, max 10 (EU SMPC)− 15 (USPI) g/day<br>• or<br>• Up-titrate[b,c] SZC, if started, by 5 g once daily, to a maximum dose of 10 (EU SMPC) − 15 (USPI) g daily, until serum K+ <5.1 mmol/L, or down-titrating to 5 g every other day, depending on potassium levels. | • Suspend RAASi and re-assess serum K+ levels after 3–7 days[d]<br>• Maintain RAASi if started, but re-assess serum K+ levels after 3–7 days:[d]<br>– If K+ levels are still high and SZC is on maximum dose, consider RAASi down-titration[d]<br>– If K+ levels < 5.1 mmol/L, consider up-titration of RAASi if not on guideline-recommended target dose[d] | • After initiating[a] or changing SZC dose, measure serum K+ and creatinine within 3–7 days[†] and repeat after 1 week. If target K+ value is achieved, measure serum K+ at 1 month, then every 3 months<br>• Any time that a change in electrolyte or volume status[f] is suspected, eg due to gastrointestinal problems, re-measure serum K+ and creatinine and repeat the above monitoring sequence as per standard clinical practice and applicable guideline recommendations<br>• **as SZC mechanism of action involves potassium exchange for sodium (or hydrogen) in the GI tract, monitor edema during SZC therapy particularly in patients prescribed a SZC dose higher than 10 g daily[f],**<br>†Monitoring frequency should be individualised based on the clinical situation. Some clinical scenarios may require a change in the frequency of monitoring; refer to applicable guidelines for recommendations. |
| Moderate hyperkalaemia | 5.6–5.9 | | | |
| Mild hyperkalaemia | 5.1–5.5 | • Consider initiation[a] of SZC at 10 g thrice daily for 24, 48, or 72 h (i.e. until normakalaemia), then proceed to the maintenance phase, starting with 5 g/day, then uptitrating to max 10 (EU SMPC) − 15 (USPI) g/day, or down-titrating to 5 g every other day, depending on potassium levels.<br>• or<br>• Maintain / up-titrate[c] SZC, if started, to a maximum dose of 10 g daily, until serum K+ <5.1 mmol/L | • Initiate / maintain RAASi at guideline-recommended target dose and re-assess serum K+ levels after 7 days[d]<br>• Consider up-titration of RAASi to guideline-recommended target dose[d] depending on the clinical situation and if SZC has been started[a] | |
| Normokalaemia | 4.1–5.0 | • If started on SZC, maintain dose | • Initiate / maintain / up-titrate RAASi to guideline-recommended target dose and re-assess serum K+ levels after 3–7 days[d] | |
| Mild hypokalaemia | 3.5–4.0 | • Stop SZC[e] if on lowest (5 g every other day) dose, or<br>• Down-titrate[c] SZC at ≥ 7-day intervals by 5 g once daily | | |
| Hypokalaemia | < 3.5 | • Stop temporarily until K is above 3.5 (or 4.0 if you want to be conservative) then restart at lower dose. Stop if patient was already on 5 g every other day.[b,e] | | |

# STRONG-HF

## Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

Prof Alexandre Mebazaa, MD • Beth Davison, PhD • Prof Ovidiu Chioncel, MD • Prof Alain Cohen-Solal, MD • Rafael Diaz, MD • Prof Gerasimos Filippatos, MD • et al. Show all authors

Published: November 07, 2022 • DOI: https://doi.org/10.1016/S0140-6736(22)02076-1 •

The 2021 European Society of Cardiology Heart Failure Association guidelines for the treatment of heart failure recommend follow-up of patients after an acute heart failure admission within 2–4 weeks after discharge and initiation of recommended therapies, but the level of evidence for this recommendation is low. Furthermore, frequency and content of visits and the dose to which medications should be titrated during those visits are not clearly specified in these guidelines.

Additionally, oral heart failure medications such as β blockers; angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors; and mineralocorticoid receptor antagonists have been shown to be beneficial for the long-term outcomes of patients with chronic stable heart failure. However, how to safely optimise oral heart failure medications during the so-called vulnerable phase after discharge from hospital after acute heart failure is unknown. Retrospective analyses and some prospective studies, which were mostly small and underpowered for significant adverse events such as readmissions and death, and registries of different strategies, have not given conclusive results.

**STRONG-HF:**

- Multinational, open-label, randomised, parallel-group trial;
- Patients aged 18–85 years admitted to hospital with acute heart failure, **not treated with full doses of guideline-directed drug treatment**;
- Recruitement from 87 hospitals in 14 countries;
- Before discharge, eligible patients were randomly assigned (1:1) to either usual care or high-intensity care;
- Stratified by left ventricular ejection fraction (≤40% vs >40%) and country;
- **Usual care** followed usual **local practice**;
- **High-intensity care** involved the **up-titration of treatments to 100% of recommended doses within 2 weeks of discharge** and four scheduled outpatient visits over the 2 months after discharge that closely monitored clinical status, laboratory values, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations.

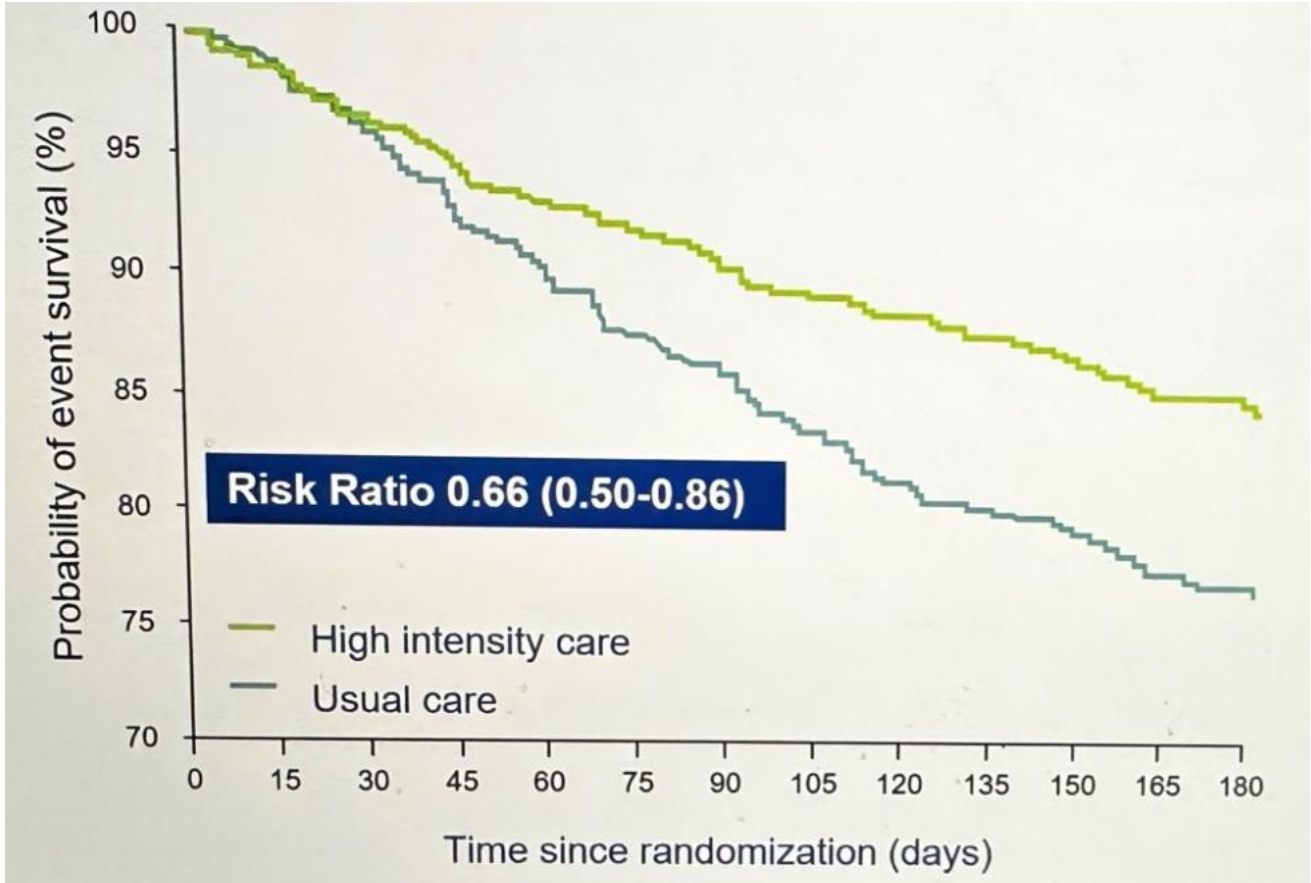
**INCLUSION CRITERIA:**

- Age 18-85 years old
- Admission within 72 hours before screening for acute HF
- Hemodynamically stable
- NT-proBNP >2500 pg/mL and 10% decrease between screening and before randomization (but still > 1500 pg/mL)
- Without treatment of optimal doses of oral HF therapies within 2 days before hospital discharge

**EXCLUSION CRITERIA:**

- Intolerance to beta-blockers, ACE inhibitors, or ARBs

**PRIMARY ENDPOINT:** 180-day readmission to hospital due to heart failure or all-cause death.




Heart failure readmission or all-cause death up to day 180 occurred in 74 (15·2% down-weighted adjusted Kaplan-Meier estimate) of 506 patients in the high-intensity care group and 109 (23·3%) of 502 patients in the usual care group (adjusted risk difference 8·1% [95% CI 2·9–13·2]; p=0·0021; risk ratio 0·66 [95% CI 0·50–0·86]).

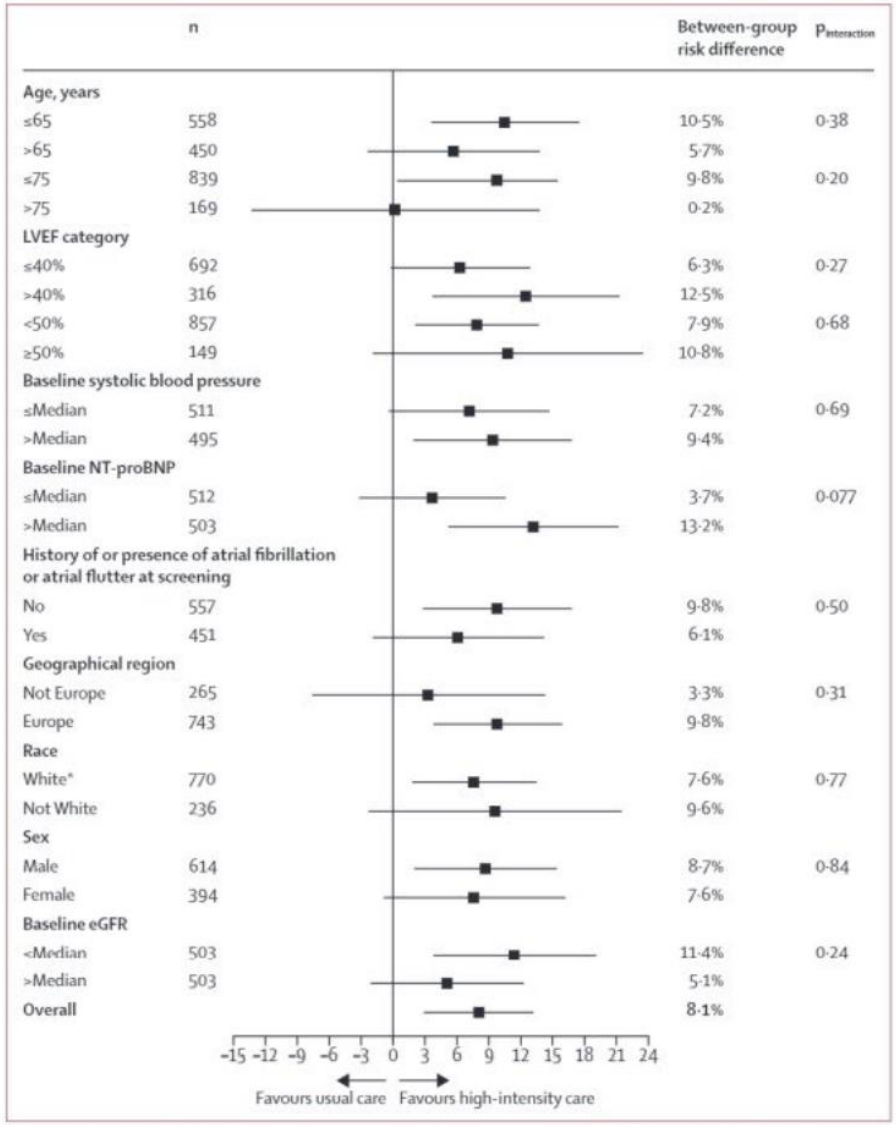



***Figure 4:*** **Prespecified and post-hoc subgroup analysis of primary endpoint (difference in 180-day risk of all-cause death or heart failure readmission)**

Median systolic blood pressure was 120 mm Hg, median NT-proBNP concentration was 2859 pg/mL, and median eGFR was 59·40 mL/min per 1·7 3m². eGFR=estimated glomerular filtration rate. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro-B-type natriuretic peptide. *Includes self-reported White or Caucasian.

| | High-intensity care group (n=542) | Usual care group (n=536) | Adjusted treatment effect (95% CI) | Adjusted risk ratio (95% CI) | p value |
|---|---|---|---|---|---|
| **Primary endpoint** | | | | | |
| All-cause death or heart failure readmission by day 180* | 74/506 (15·2%) | 109/502 (23·3%) | 8·1 (2·9 to 13·2) | 0·66 (0·50 to 0·86) | 0·0021 |
| **Secondary endpoints** | | | | | |
| Change from baseline to day 90 in EQ-5D VAS† | 10·72 (0·88) | 7·22 (0·90) | 3·49 (1·74 to 5·24) | NA | <0·0001 |
| All-cause death by day 180* | 39/506 (8·5%) | 48/502 (10·0%) | 1·6 (−2·3 to 5·4) | 0·84 (0·56 to 1·26) | 0·42 |
| All-cause death or heart failure readmission by day 90* | 55 (10·4%) | 72 (13·8%) | 3·4 (−0·4 to 7·3) | 0·73 (0·53 to 1·02) | 0·081 |
| **Prespecified exploratory endpoints** | | | | | |
| Cardiovascular death by day 180* | 32/506 (6·9%) | 44/502 (9·3%) | 2·4 (−1·2 to 6·1) | 0·74 (0·47 to 1·16) | 0·19 |
| Cardiovascular death by day 90* | 17 (3·3%) | 28 (5·4%) | 2·1 (−0·3 to 4·6) | 0·60 (0·33 to 1·09) | 0·086 |
| All-cause death by day 90* | 23 (4·3%) | 30 (5·7%) | 1·4 (−1·2 to 4·0) | 0·76 (0·45 to 1·29) | 0·28 |
| Heart failure readmission by day 180* | 47/506 (9·5%) | 74/502 (17·1%) | 7·6 (3·0 to 12·1) | 0·56 (0·38 to 0·81) | 0·0011 |
| Heart failure readmission by day 90* | 36 (6·9%) | 48 (9·5%) | 2·5 (−0·8 to 5·8) | 0·67 (0·43 to 1·04) | 0·13 |
| Finkelstein-Schoenfeld hierarchical composite‡ | .. | .. | 1·28 (1·13 to 1·46) | NA | 0·0002 |
| Proportion of comparisons where group is superior§ | 40·4% | 29·4% | .. | .. | .. |
| Proportion of comparisons where groups are tied | 30·2% | NA | .. | .. | .. |
| **Sensitivity analyses** | | | | | |
| All-cause death or heart failure readmission by day 180, excluding COVID-19 deaths* | 69/506 (14·1%) | 108/502 (23·0%) | 8·9 (3·9 to 14·0) | 0·61 (0·46 to 0·82) | 0·0005 |
| All-cause death by day 180, excluding COVID-19 deaths* | 33/506 (7·1%) | 47/502 (9·8%) | 2·7 (−1·0 to 6·4) | 0·72 (0·47 to 1·12) | 0·15 |

Data are n (adjusted Kaplan-Meier %), n/N (down-weighted adjusted Kaplan-Meier %), or mean (SD), unless otherwise stated. For 180-day outcomes, results for patients in cohort 1 are down-weighted proportional to half its sample size. For 90-day outcomes, cohort 1 is fully weighted. LVEF=left ventricular ejection fraction. NA=not applicable. VAS=visual analogue scale. *Kaplan-Meier estimated cumulative risks adjusted for LVEF (≤40% vs >40%) and geographical region using Mantel-Haenszel weights are shown for each treatment group. Treatment effect is the adjusted risk difference between treatment groups. †Analysis of change in EQ-5D VAS is based on available data and excludes patients from Mozambique because of the unavailability of a linguistically validated translation of the EQ-5D VAS in that country (ie, analysis includes n=461 from the high-intensity care group and n=454 the from usual care group). Statistics are estimated from an ANCOVA model with fixed terms for treatment, LVEF (≤40% vs >40%), geographical region, and baseline value. Treatment effect is the adjusted mean difference between treatment groups. ‡Treatment effect is the Mann-Whitney odds adjusted for LVEF (≤40% vs >40%) and geographical region, using Mantel-Haenzsel weights. p value calculated from van Elteren's test stratified by LVEF (≤40% vs >40%) and geographical region, using modified ridit scores. A Mann-Whitney odds value of >1·0 favours high-intensity care. §Proportion of 78 666 total pairwise patient comparisons within strata where outcome in given treatment group is superior.

*Table 3:* **Primary, secondary, and exploratory analyses**

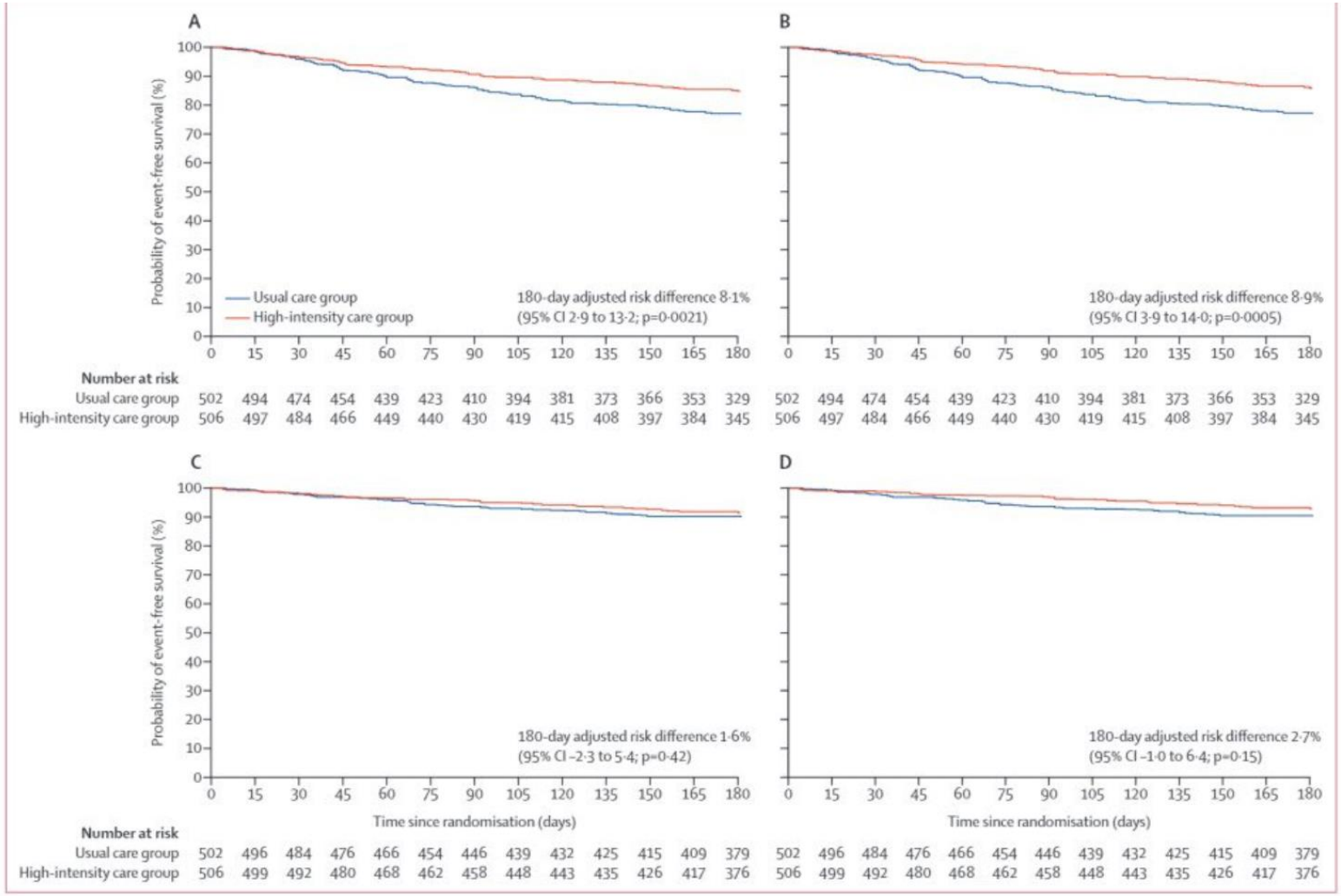



***Figure 3*: Adjusted Kaplan-Meier estimates of cumulative event-free survival with down-weighting of cohort 1 for all-cause death or heart failure readmission (A), all-cause death or heart failure excluding deaths due to COVID-19 (B), all-cause mortality (C), and all-cause mortality excluding deaths due to COVID-19 (D), from randomisation up to day 180**
Adjusted 180-day risk differences are given. Analyses excluding COVID-19-related deaths were prespecified sensitivity analyses.

An **intensive treatment strategy of rapid up-titration of guideline-directed medication** and close follow-up after an acute heart failure 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 heart failure readmission compared with usual care.**

More adverse events by 90 days occurred in the high-intensity care group (223 [41%] of 542) than in the usual care group (158 [29%] of 536) but similar incidences of serious adverse events (88 [16%] *vs* 92 [17%]) and fatal adverse events (25 [5%] *vs* 32 [6%]) were reported in each group.

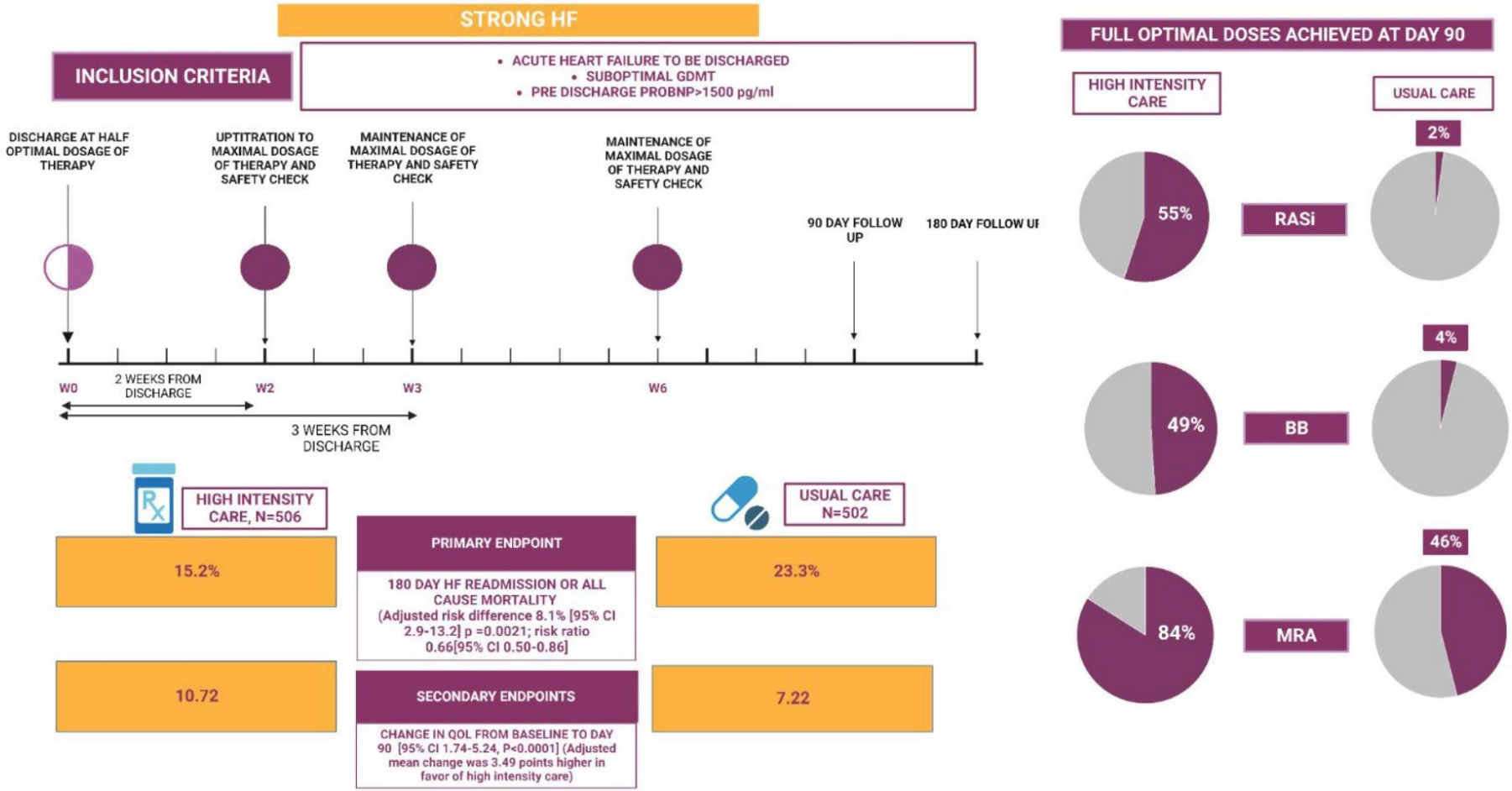
By day 90, blood pressure, pulse, New York Heart Association class, bodyweight, and NT-proBNP concentration had **decreased** more in the high-intensity care group than in the usual care group.

The **study was stopped early per the data and safety** monitoring board's recommendation because of greater than expected between-group differences.

## STRONG–HF SUMMARY

- Reduced death/HF hospitalization, with large absolute risk reduction;
- Improved patient-reported health status and NYHA class;
- Improved congestion;
- No significant difference in serious adverse events compared with usual care.

Millions of people are admitted to hospital for acute heart failure worldwide each year, with a substantial risk of rehospitalisation or death within 3–6 months of admission; therefore, **the results of the STRONG-HF trial might have a substantial impact on clinical practice and, if adopted and implemented worldwide, on outcomes for patients with heart failure**.


STRONG HF
INCLUSION CRITERIA
• ACUTE HEART FAILURE TO BE DISCHARGED
• SUBOPTIMAL GDMT
• PRE DISCHARGE PROBNP>1500 pg/ml
DISCHARGE AT HALF OPTIMAL DOSAGE OF THERAPY
UPTITRATION TO MAXIMAL DOSAGE OF THERAPY AND SAFETY CHECK
MAINTENANCE OF MAXIMAL DOSAGE OF THERAPY AND SAFETY CHECK
MAINTENANCE OF MAXIMAL DOSAGE OF THERAPY AND SAFETY CHECK
90 DAY FOLLOW UP
180 DAY FOLLOW UI
W0
2 WEEKS FROM DISCHARGE
W2
W3
W6
3 WEEKS FROM DISCHARGE
HIGH INTENSITY CARE, N=506
USUAL CARE N=502
15.2%
23.3%
PRIMARY ENDPOINT
180 DAY HF READMISSION OR ALL CAUSE MORTALITY
(Adjusted risk difference 8.1% [95% CI 2.9-13.2] p =0.0021; risk ratio 0.66[95% CI 0.50-0.86]
10.72
7.22
SECONDARY ENDPOINTS
CHANGE IN QOL FROM BASELINE TO DAY 90 [95% CI 1.74-5.24, P<0.0001] (Adjusted mean change was 3.49 points higher in favor of high intensity care)
FULL OPTIMAL DOSES ACHIEVED AT DAY 90
HIGH INTENSITY CARE
USUAL CARE
55%
RASi
2%
49%
BB
4%
84%
MRA
46%
RAPID UP-TITRATION OF HF THERAPIES UNDER CLOSE FOLLOW UP IS SAFE AND REDUCES READMISSIONS DUE TO HF OR ALL CAUSE DEATHS AND IMPROVES QOL

# OBRIGADA PELA VOSSA ATENÇÃO!