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ORIGINAL RESEARCH

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ESC European Society of Cardiology

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RESEARCH ARTICLE

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Research Article

Salt repletion and diuretic response: The role of serum chloride. A post-hoc analysis of the SALT-HF trial on furosemide and hypertonic saline solution administration in ambulatory patients with worsening heart failure

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JAMA | Original Investigation

Early Intervention in Patients With Asymptomatic Severe Aortic Stenosis and Myocardial Fibrosis

The EVOLVED Randomized Clinical Trial

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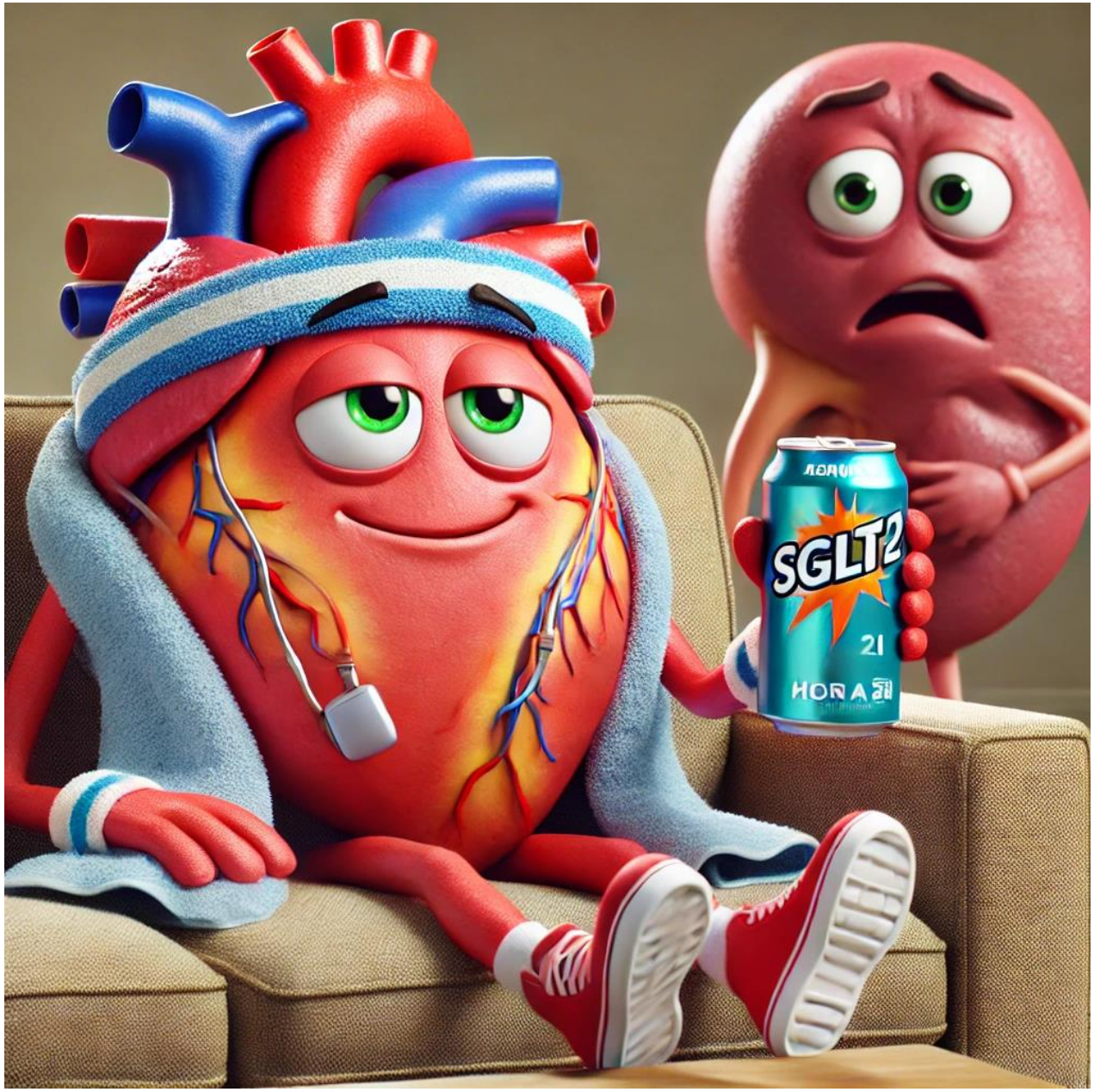
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SGLT2 Inhibitor Therapy in Patients With Transthyretin Amyloid Cardiomyopathy

BACKGROUND Transthyretin cardiomyopathy (ATTR-CM) was an exclusion criterion in randomized clinical trials of sodium-glucose cotransporter 2 inhibitors (SGLT2i).

OBJECTIVES This study sought to assess the effectiveness and tolerability of SGLT2i in patients with ATTR-CM.

METHODS Data of 2,356 consecutive ATTR-CM patients (2014-2022) were analyzed: 260 (11%) received SGLT2i. After comparing the groups according to the treatment, 14 variables were significantly different—age and N-terminal pro-B-type natriuretic peptide were included in the model. A propensity score reflecting the likelihood of being treated with SGLT2i for each patient was determined using 16 variables.

FIGURE 1 Diagram of the Study With the Propensity Score Matching Process

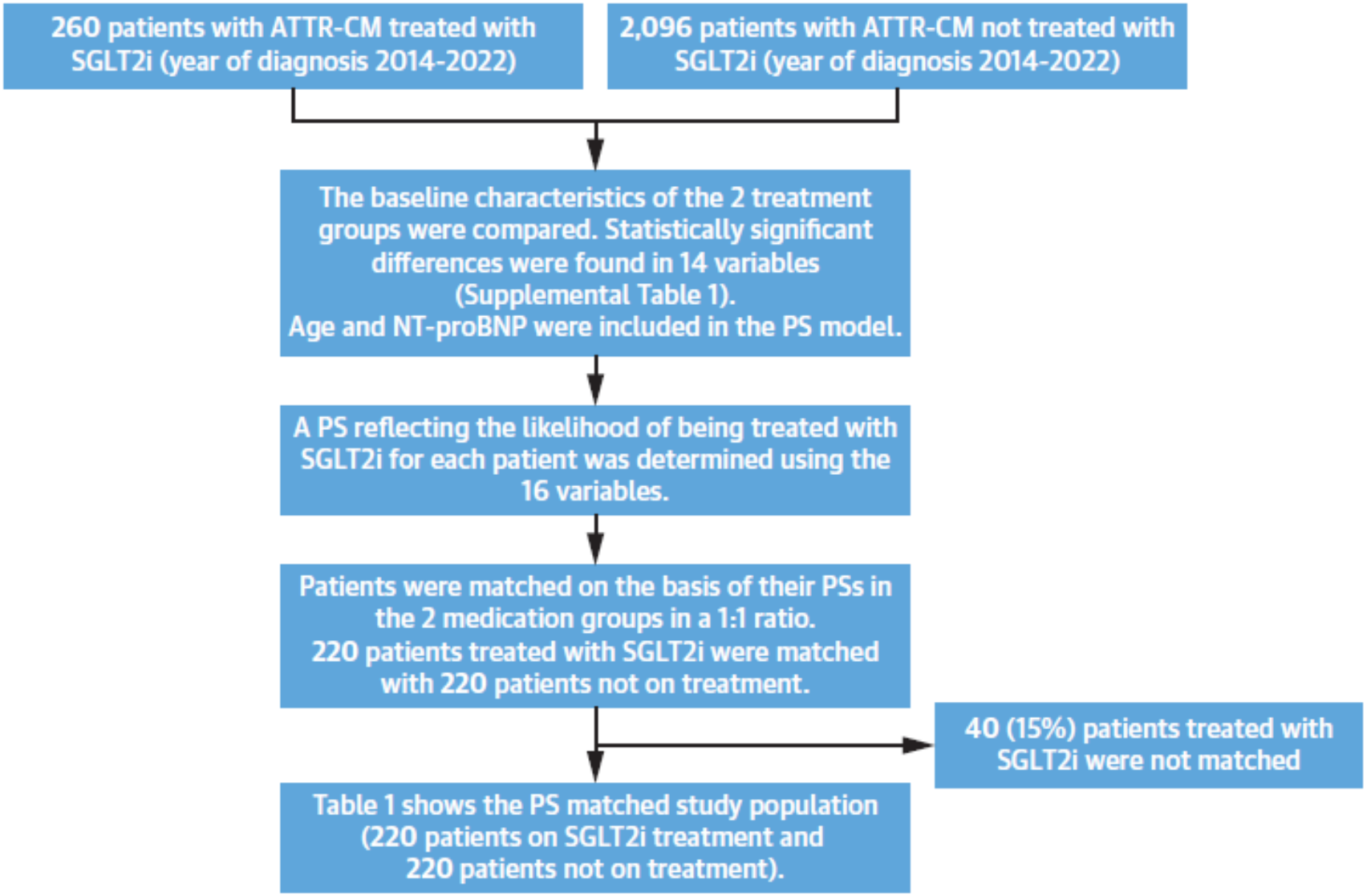


TABLE 1 Characteristics of the Propensity Score-Matched Study Population

	All (N = 440)	No SGLT2i (n = 220)	SGLT2i (n = 220)	MSD
Age, y	77 ± 7.6	76.7 ± 7.7	77.2 ± 7.5	-0.061
Male	89.8 (395)	89.1 (196)	90.5 (199)	0.051
Year of diagnosis ≥2018	90.5 (398)	92.3 (203)	88.6 (195)	0.123
Baseline SBP, mm Hg	126 (113-138)	129 (116-141)	122 (111-135)	0.251
wtATTR	80.7 (355)	79.1 (174)	82.3 (181)	0.075
hATTR	19.3 (85)	20.9 (46)	17.7 (39)	0.075
Atrial fibrillation	66.6 (293)	65.9 (145)	67.3 (148)	0.066
IHD	17.0 (75)	18.6 (41)	15.5 (34)	0.084
Diabetes mellitus	41.6 (183)	42.7 (94)	40.5 (89)	0.060
Hypertension	57.7 (254)	57.3 (126)	58.2 (128)	-0.012
Heart failure severity				
NYHA functional class				0.029
I	10.9 (48)	10.5 (23)	11.4 (25)	
II	66.4 (292)	66.8 (147)	65.9 (145)	
III	21.8 (96)	21.8 (48)	21.8 (48)	
IV	0.9 (4)	0.9 (2)	0.9 (2)	
Missing	0 (0)			
NAC stage				0.057
1	43.6 (192)	44.5 (98)	42.7 (94)	
2	35.0 (154)	33.6 (74)	36.4 (80)	
3	21.4 (94)	21.8 (48)	20.9 (46)	
Missing	0 (0)			
NT-proBNP, pg/L	2,693 (1,662-5,052)	2,815 (1,763-5,042)	2,625 (1,448-5,250)	0.053
eGFR, mL/min/1.73 m^2	56 ± 18	55 ± 17	56 ± 18	-0.088
Hemoglobin, mg/dL	136 (125-147)	133 (123-146)	136 (126-147)	-0.071
Echocardiographic parameters				
EDD, mm	44 (40-48)	44 (41-48)	45 (40-48)	0.083
MWT, mm	18 ± 2.9	17.9 ± 2.8	18.1 ± 3.0	0.084
LVEF, %	46.0 ± 10.6	46.0 ± 10.2	45.8 ± 11.0	0.019
LVEF ≤40%	34.1 (150)	31.8 (70)	36.4 (80)	0.096
E/e′	17.9 ± 5.8	18.3 ± 6	17.5 ± 5	0.080
TAPSE, mm	15 (12-18)	15 (12-19)	15 (12-18)	0.078
Medications				
Loop diuretic agents	84.3 (371)	84.1 (185)	84.5 (186)	0.012
ACEI/ARB	45.5 (200)	46.4 (102)	44.5 (98)	0.036
Beta-blockers	60.5 (266)	61.8 (136)	59.1 (130)	0.055
MRA	46.6 (205)	46.8 (103)	46.4 (102)	0.009
Disease-modifying therapy	21.4 (94)	21.8 (48)	20.9 (46)	0.020

Study Design and Population

2,356 patients with ATTR-CM

Propensity score matching in a 1:1 ratio utilizing 16 variables

220 patients with ATTR-CM treated with SGLT2i

220 matched untreated controls with ATTR-CM

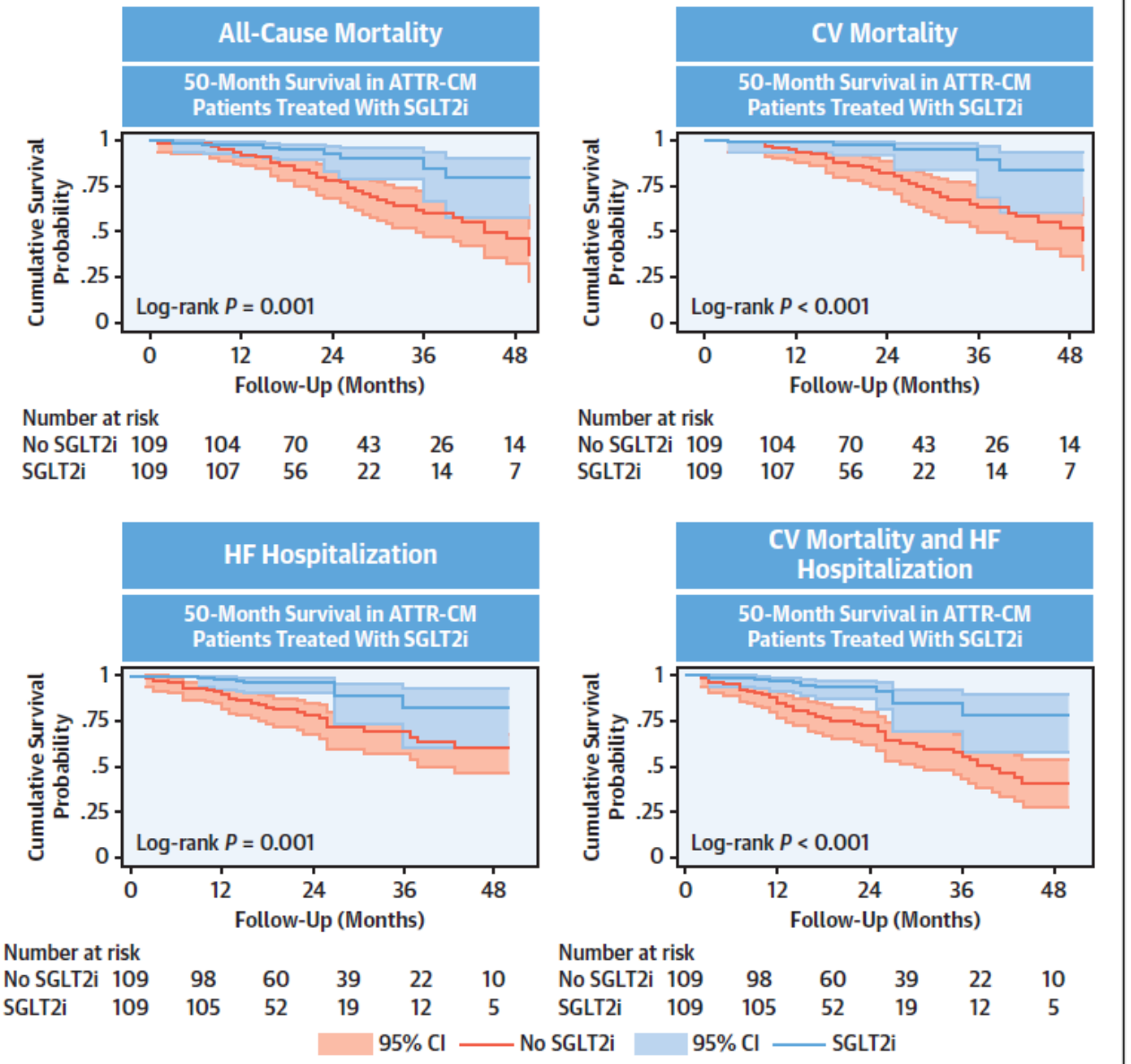
Main Findings

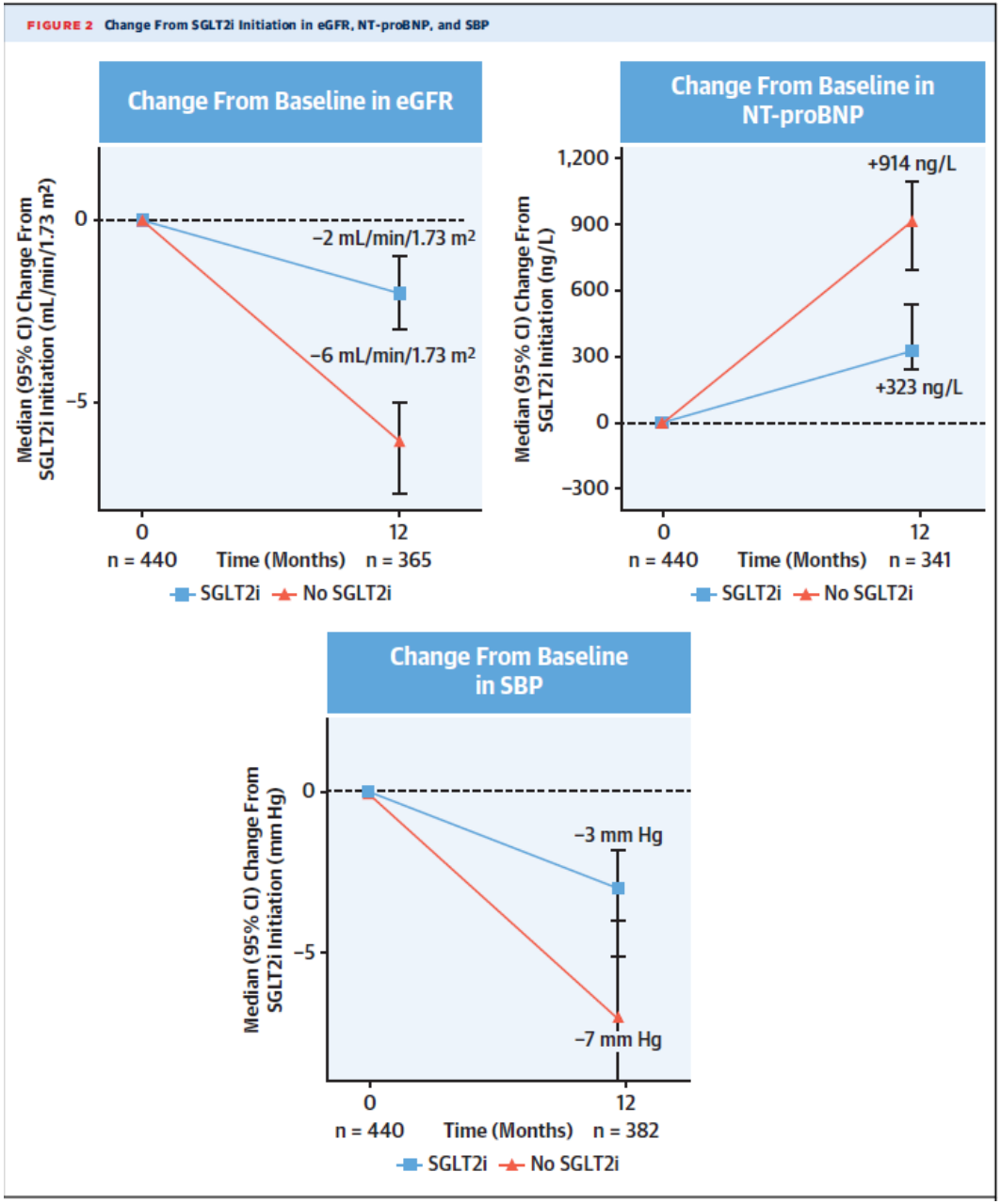
Safe treatment: 4.5% discontinuation rate over 28 months

- All-cause mortality
- Cardiovascular mortality
- HF hospitalization
- Cardiovascular mortality and HF hospitalization

- Slower decline in eGFR
- Attenuated rise in NT-proBNP
- Lower loop diuretic requirement
- Stable blood pressure profile

FIGURE 3 Survival and HF Hospitalizations in ATTR-CM According to SGLT2i Treatment

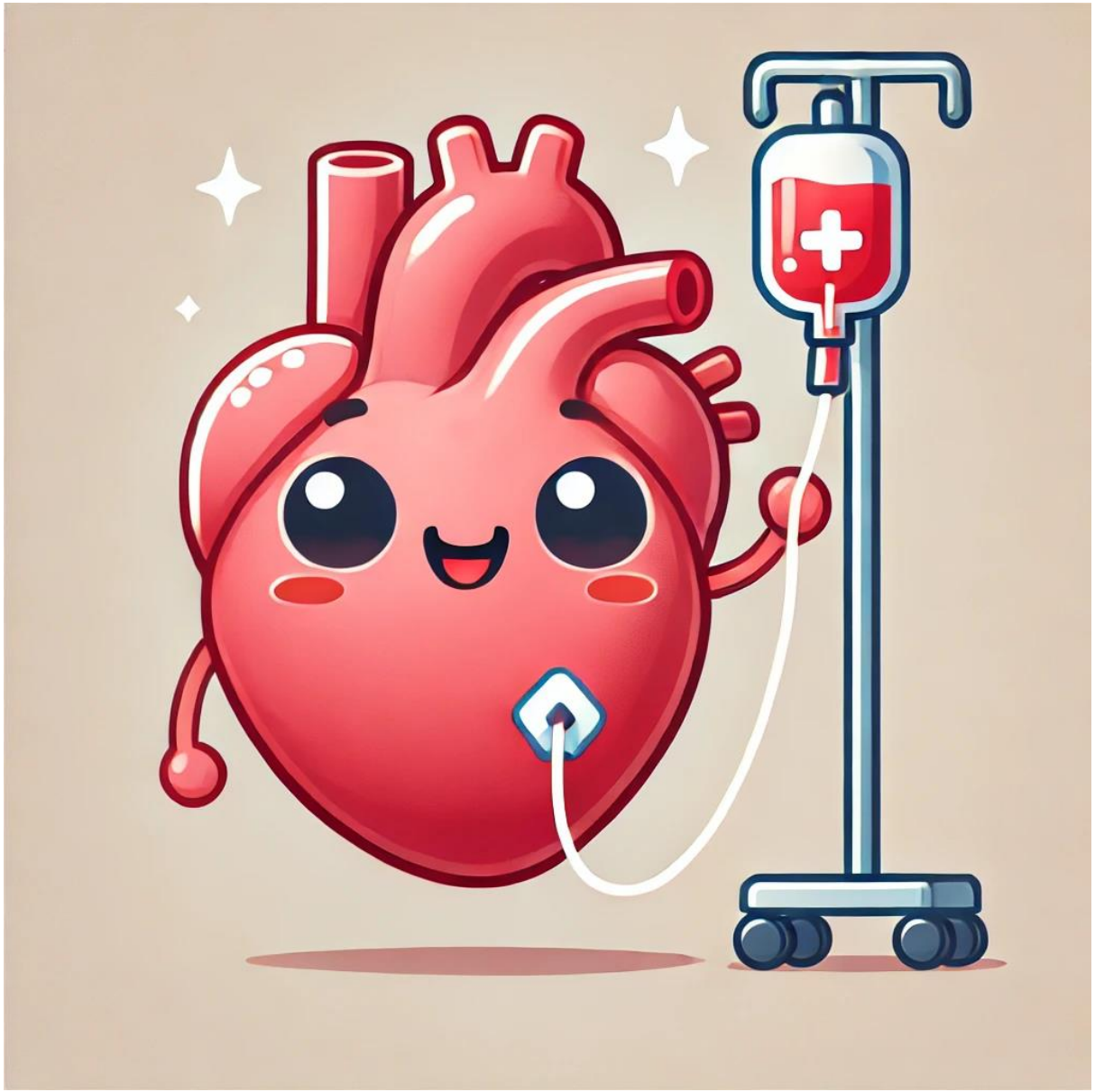




SGLT2 Inhibitor Therapy in Patients With Transthyretin Amyloid Cardiomyopathy

CONCLUSIONS

In this large cohort of patients with ATTR-CM, SGLT2i treatment was well tolerated, with only 4.5% of patients discontinuing therapy, and was associated with a decreased rate of worsening in symptoms, less increase in NT-proBNP, slower decline in renal function, and reduced new loop diuretic agent dose initiation. During follow-up, treatment with SGLT2i was associated with a reduced risk of all-cause mortality, cardiovascular mortality, HF hospitalization, and the composite of cardiovascular mortality and HF hospitalization. In the absence of randomized trials, these data may inform clinicians regarding the use of SGLT2i in patients with ATTR-CM.



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RESEARCH ARTICLE

Efficacy and safety of hypertonic saline therapy in ambulatory patients with heart failure: The SALT-HF trial

- La IC es una condición prevalente con alta morbilidad y mortalidad
- La congestión y la resistencia a los diuréticos son desafíos comunes en el manejo de la IC
- El SSH ya ha demostrado beneficios en pacientes hospitalizados.

TIPO DE ESTUDIO: ensayo multicéntrico, doble ciego, aleatorizado.

OBJETIVO DEL ESTUDIO:

- Evaluar la eficacia y seguridad de la combinación del SSH con furosemida intravenosa en pacientes ambulatorios con IC descompensada

POBLACION: Pacientes ambulatorios con IC descompensada que requieren diuréticos intravenosos desde dic 20 a marzo 23 en 13 hospitales españoles

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CRITERIOS DE INCLUSION:

- Paciente con IC descompensada que no requieren hospitalización
- Presencia de al menos dos signos de sobrecarga de volumen (edema periférico, IY, ascitis, derrame pleural)

CRITERIOS DE EXCLUSION:

- Hiponatremia severa
- Insuficiencia renal aguda
- Hipotensión significativa

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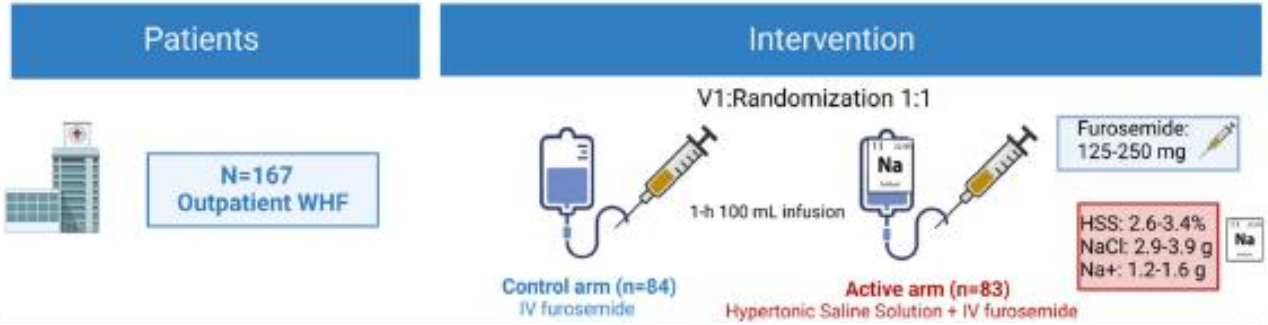

- 13 centros
- españoles

- Edad media 81 años

- 30,5%mujeres

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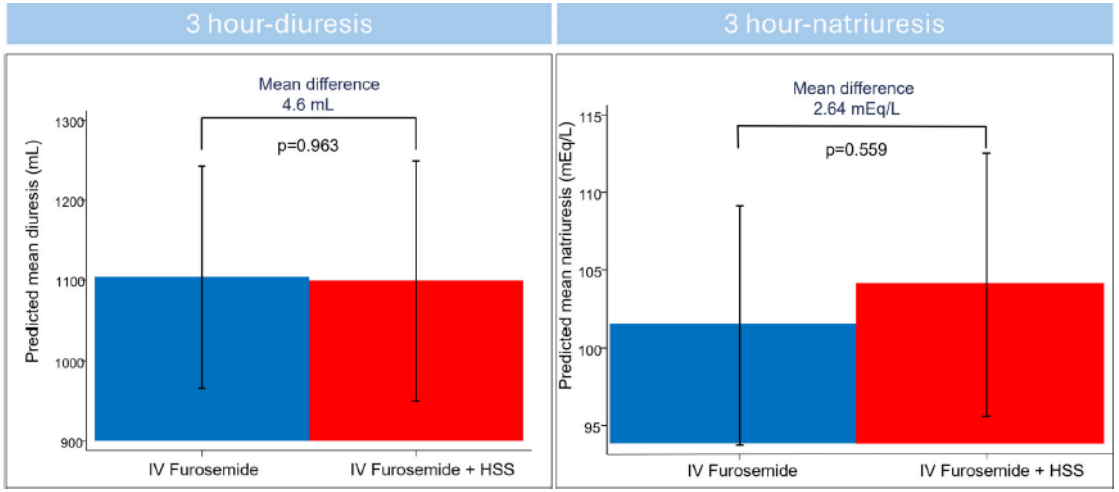
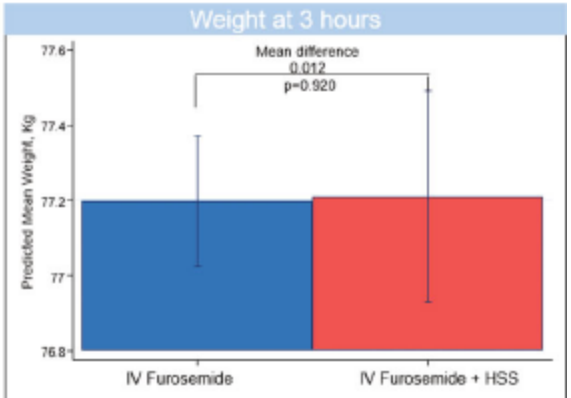
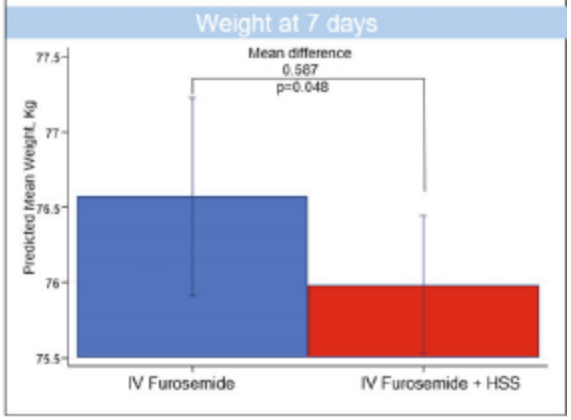
OBJETIVOS PRINCIPALES:

1. Diuresis a las 3 horas: no hubo diferencias significativas
2. Natriuresis a las 3 horas: resultados similares
3. Peso corporal a los 7 días: reducción significativa en el grupo SSH + furosemida







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OBJETIVOS SECUNDARIOS:

- Parámetros de congestión: no se observaron diferencias significativas en la puntuación de congestión clínica, diámetro de la vena cava inferior o líneas B en ecografía pulmonar

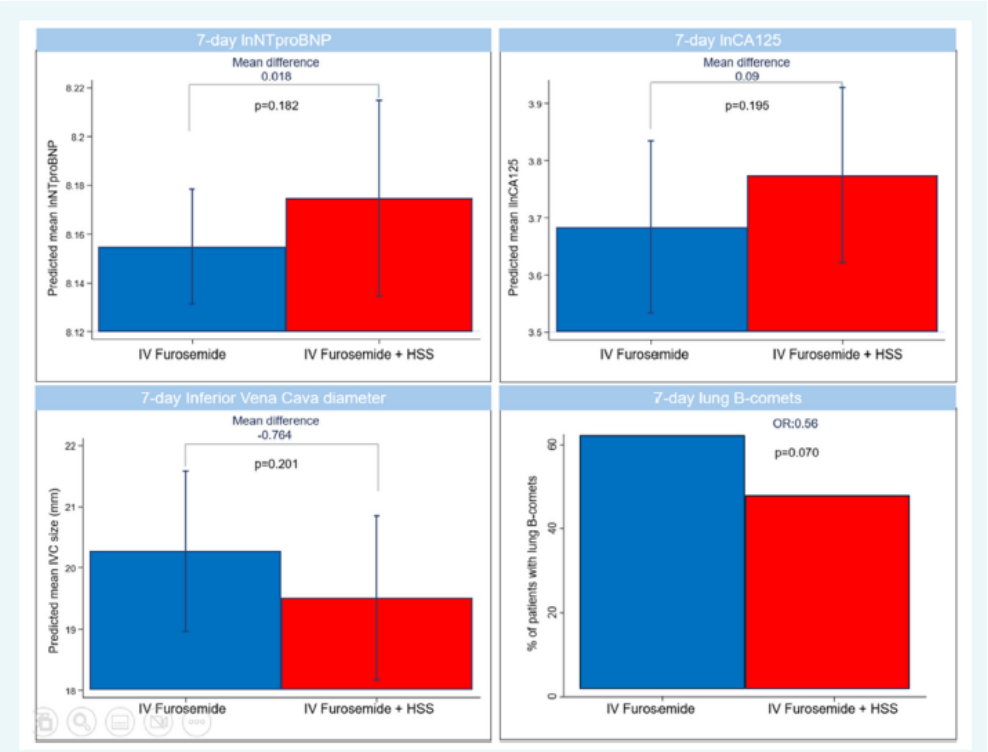

Figure 4 Change in 7-day natural logarithm (ln) N-terminal pro-B-type natriuretic peptide (NT-proBNP), cancer antigen 125 (CA125), inferior vena cava (IVC) diameter, and lung ultrasound B-lines. HSS, hypertonic saline solution; IV, intravenous.

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-Eventos clínicos a los 30 días: incidencia similar de empeoramiento de la insuficiencia cardiaca y hospitalizaciones entre ambos grupos

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SEGURIDAD:

- No se observaron diferencias significativas en la función renal o desequilibrios electrolíticos entre los grupos
- Eventos adversos: la terapia mostró perfil de seguridad adecuado

Safety Endpoints

Endpoint	Active Arm	Control Arm	*P* value
WRF, n(%)	12 (14)	9 (11)	0.642
Hypokalemia, n(%)	6 (7.3)	10 (12.5)	0.303
Hyperkalemia, n(%)	1 (1)	0 (0)	-
WHF, n(%)	22 (26.5)	28 (33.3)	HR: 0.76 (0.43- 1.33) *P*=0.330
Death/HF-hospitalization, n(%)	5 (6)	7 (8)	HR: 0.69 (0.22- 2.16) *P*=0.521

Hypertonic therapy showed an appropriate safety profile

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CONCLUSIONES.

Una sola infusión de furosemida intravenosa con SSH no mejoró la diuresis a las tres horas, ni los parámetros de congestión en pacientes ambulatorios con IC descompensada

Se observó una reducción de peso a los 7 días en el grupo SSH, pero sin diferencias en otros parámetros clínicos.

La combinación de furosemida y SSH fue segura, pero no mostró beneficios adicionales en comparación con furosemida sola.

Se requieren mas estudios para evaluar diferentes concentraciones de SSH, frecuencias de administración o poblaciones de pacientes.

European Journal of
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Research Article

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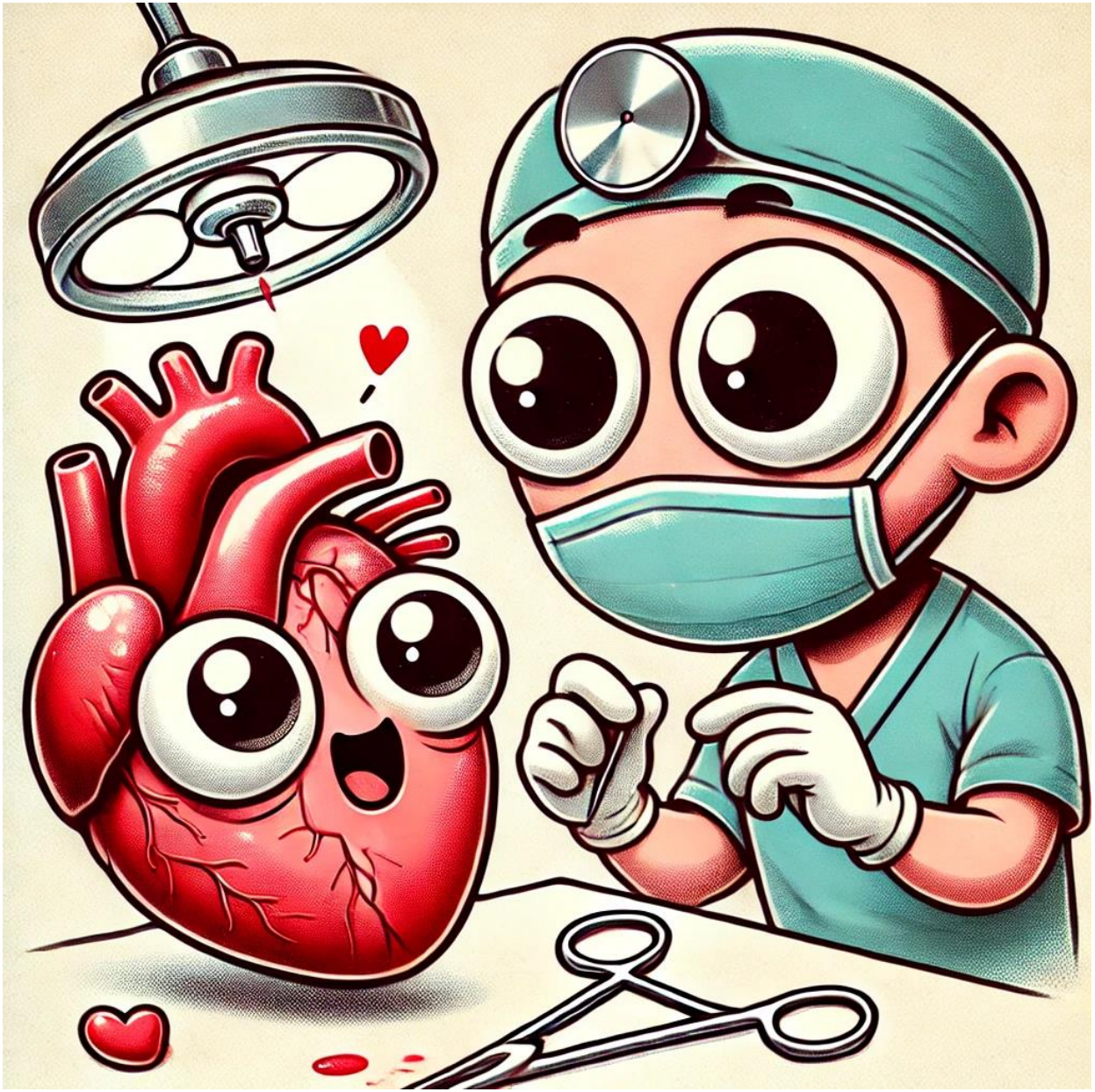
La hipocloremia parece ser un marcador de menor respuesta a la diuresis y peor evolución en insuficiencia cardíaca. La administración de solución salina hipertónica junto con furosemida podría mejorar la natriuresis en pacientes con hipocloremia, lo que podría traducirse en una mejor descompensación a corto plazo.

Estos hallazgos sugieren que la suplementación con cloruro podría ser una estrategia útil para superar la resistencia a los diuréticos en pacientes con insuficiencia cardíaca y hipocloremia. Además, resaltan la necesidad de monitorizar los niveles de cloruro en estos pacientes como parte de la evaluación terapéutica.



JAMA | Original Investigation

Early Intervention in Patients With Asymptomatic Severe Aortic Stenosis and Myocardial Fibrosis
The EVOLVED Randomized Clinical Trial

IMPORTANCE Development of myocardial fibrosis in patients with aortic stenosis precedes left ventricular decompensation and is associated with an adverse long-term prognosis.

OBJECTIVE To investigate whether early valve intervention reduced the incidence of all-cause death or unplanned aortic stenosis–related hospitalization in asymptomatic patients with severe aortic stenosis and myocardial fibrosis.

DESIGN, SETTING, AND PARTICIPANTS This prospective, randomized, open-label, masked end point trial was conducted between August 2017 and October 2022 at 24 cardiac centers across the UK and Australia. Asymptomatic patients with severe aortic stenosis and myocardial fibrosis were included. The final date of follow-up was July 26, 2024

INTERVENTION Early valve intervention with transcatheter or surgical aortic valve replacement or guideline-directed conservative management.

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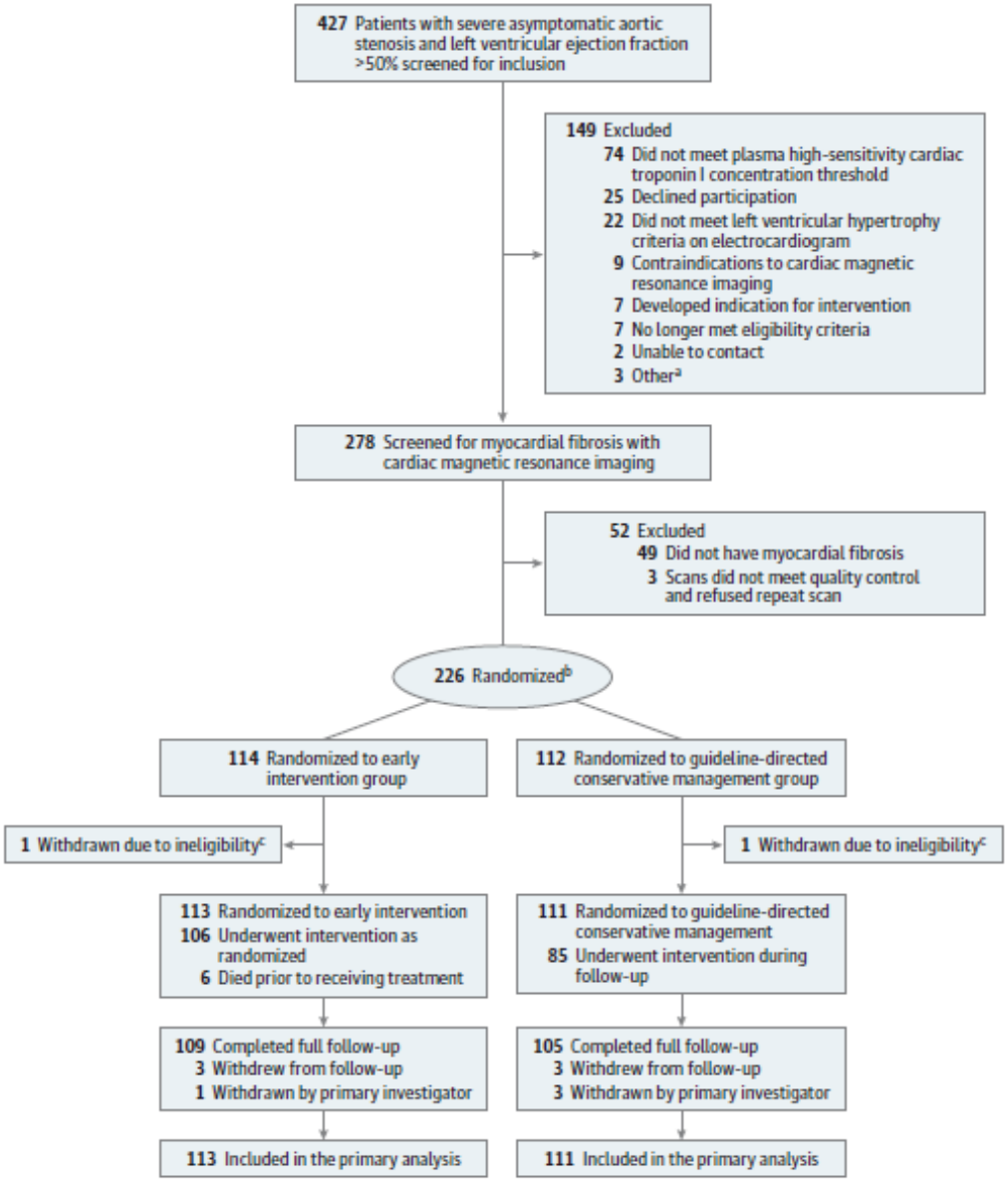
Figure 1. Recruitment, Randomization, and Follow-Up in the EVOLVED Trial



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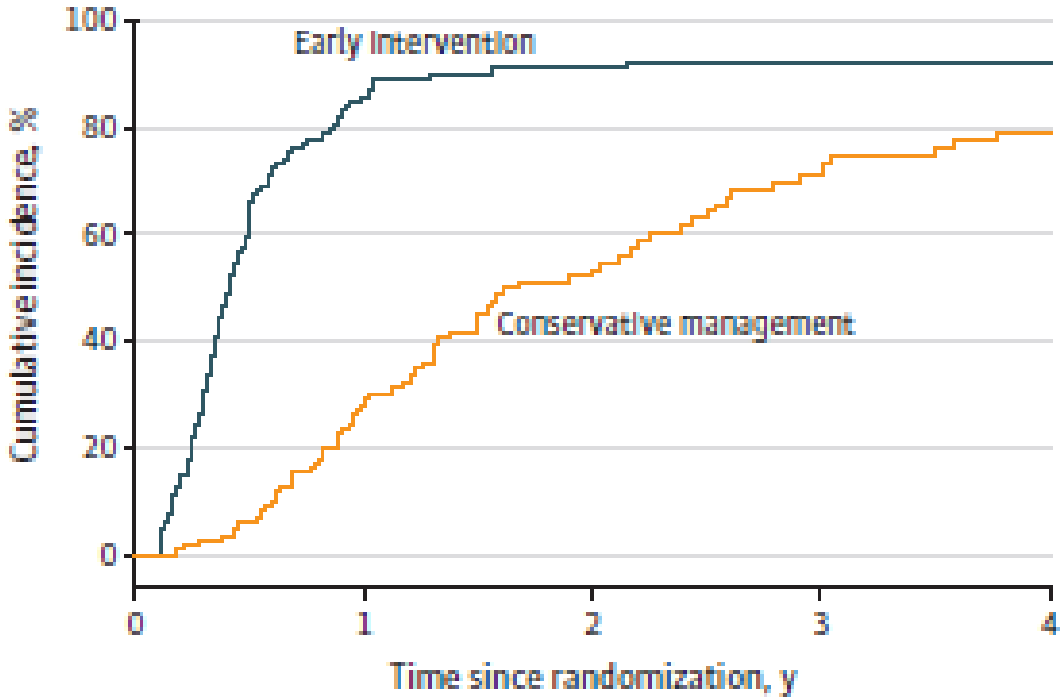
Early Intervention in Patients With Asymptomatic Severe Aortic Stenosis and Myocardial Fibrosis
The EVOLVED Randomized Clinical Trial

- **<u>OBJETIVO PRIMARIO</u>**: compuesto de muerte global u hospitalización no planificada relacionada con la estenosis aórtica

- **<u>OBJETIVOS SECUNDARIOS</u>**: los dos primarios y otros 7: muerte relacionada con la estenosis aórtica, necesidad de marcapasos, endocarditis, ictus, disfunción ventricular, complicaciones perioperatorias, clase funcional al año

Figure 2. Cumulative Incidence of Aortic Valve Intervention



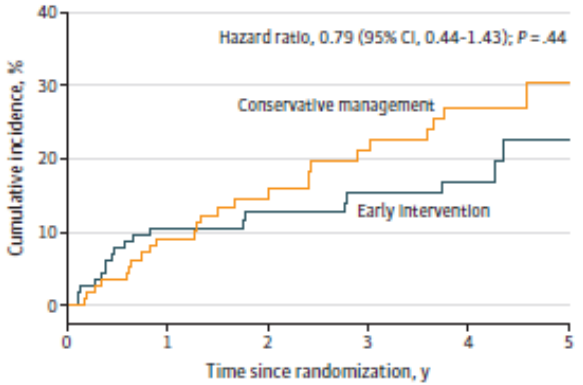
No. of patients at risk

Early Intervention	113	16	8	7	7
Conservative management	111	77	37	18	12

At 12 months, 86% of patients in the early intervention group received aortic valve intervention compared with 28% of patients in the guideline-directed conservative management group.

Figure 3. Cumulative Incidence of the Primary Composite End Point and Its Components

A All-cause death or unplanned aortic stenosis-related hospitalization



No. of patients at risk						
Early intervention	113	97	76	65	51	18
Conservative management	111	97	71	57	40	17

Table 2. Primary and Secondary End Points

Outcome[a]	No. (%)		Absolute difference (95% CI), %	Hazard ratio (95% CI)
	Early intervention (n = 113)	Conservative management (n = 111)		
Primary end point				
All-cause death or unplanned aortic stenosis–related hospitalization	20 (18)	25 (23)	−4.82 (−15.31 to 5.66) [*P* = .37]	0.79 (0.44 to 1.43) [*P* = .44]
Secondary end points				
All-cause death	16 (14)	14 (13)	1.55 (−7.37 to 10.46)	1.22 (0.59 to 2.51)
Cardiovascular death	10 (9)	8 (7)	1.64 (−5.47 to 8.75)	1.33 (0.52 to 3.36)
Aortic stenosis–related death	6 (5)	5 (5)	0.81 (−4.85 to 6.46)	1.25 (0.38 to 4.10)
Unplanned aortic stenosis–related hospitalization	7 (6)	19 (17)	−10.92 (−19.22 to 2.62)	0.37 (0.16 to 0.88)
Permanent pacemaker, cardiac resynchronization therapy, or automated cardiac defibrillator implantation	5 (4)	7 (6)	−1.88 (−7.78 to 4.02)	0.75 (0.24 to 2.37)
Stroke	8 (7)	14 (13)	−5.53 (−13.31 to 2.25)	0.62 (0.26 to 1.49)
Endocarditis	1 (1)	3 (3)	−1.82 (−5.29 to 1.66)	0.33 (0.03 to 3.14)
Development of left ventricular systolic impairment	8 (7)	11 (10)	−2.83 (−10.13 to 4.47)	0.72 (0.29 to 1.80)
Perioperative or postoperative complications within 30 d of surgery or transcatheter aortic valve intervention	15 (14)	9 (11)	5.17 (−2.89 to 13.22)	Odds ratio for ≥1 specified complication, 1.20 (95% CI, 0.50 to 2.93)
WHODAS 2.0 score at 1 y, adjusted mean[b]	3.3	4.1		Adjusted mean difference, −0.8 (95% CI, −2.0 to 0.4)
NYHA classification at 1 y				
Class I (least severe)	86 (80)	64 (62)		Odds ratio for higher NYHA classification, 0.37 (95% CI, 0.20 to 0.70)
Class II	19 (18)	30 (29)		
Class III	2 (2)	8 (8)		
Class IV (most severe)	0	1 (1)		

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Conclusions

Early aortic valve intervention has no demonstrable effect on the combined primary endpoint of all-cause death or unplanned aortic stenosis–related hospitalization compared with guideline-directed conservative management among patients with asymptomatic severe aortic stenosis and myocardial fibrosis. There was a wide 95% CI around the primary end point, with further research needed to confirm these findings.