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CASE REPORT

Dramatic disease regression in a case of HFrEF with end-stage renal failure treated with sacubitril/valsartan and SGLT2i

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Abstract

The amount of evidence for guideline-directed new heart failure (HFrEF) disease-modifying drugs in the context of chronic kidney disease (CKD) is relatively modest, especially in end-stage CKD. We report a case of dramatic reverse remodelling and disease regression in a naïve HFrEF young woman on haemodialysis treated with sacubitril/valsartan and SGLT2i. At 10-month follow-up, the patient normalized left ventricle and atrial volumes and improved ejection fraction to the normal range, assessed both by echocardiography and cardiac magnetic resonance. Cardiac biomarkers and exercise performance improved consensually. The haemodialysis protocol and the loop diuretic dose were unchanged within the whole period.

Keywords Heart failure; HFrEF; End-stage renal disease; CKD; Chronic kidney disease; Haemodialysis

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Background

In recent years, heart failure (HF) therapy has been heavily disrupted by the introduction of two new pharmacological classes: sacubitril/valsartan (SV) and the sodium-glucose transport protein inhibitors (SGLT2i). Together with beta-blockers (BB) and mineralocorticoid receptor antagonists (MRAs), these new drugs have significantly improved the prognosis of patients with HF with reduced ejection fraction (HFrEF). In 2021, this new treatment algorithm has been incorporated by HF guidelines,[1] which emphasize the importance of introducing these 'four pillars' into therapy as soon as possible to improve prognosis.[2–4] Specifically, SV reduced HF hospitalization and cardiovascular mortality compared with angiotensin-converting enzyme inhibitor (ACE-I),[5] whereas SGLT2i (predominantly dapagliflozin and empagliflozin) have emerged as safe, easy-to-use, and effective drugs in reducing mortality and HF hospitalizations in patients with both reduced[6,7] and preserved ejection fraction (EF),[8–10] as compared with placebo.

However, the amount of evidence for guideline-directed HF therapies in the context of chronic kidney disease (CKD) is relatively modest, especially in advanced CKD (Stages 4 and 5), as well as in the case of end-stage CKD. On this regard, although both SV and SGLT2i have clearly demonstrated their efficacy in reducing the worsening in renal failure in HF patients, randomized controlled trials (RCTs) leading to the broad use of these drugs have excluded patients with end-stage CKD (e.g. patients on haemodialysis).

The aim of this report is to describe the feasibility, the tolerability, and the efficacy of HF medical therapy in a patient with HFrEF and end-stage CKD on haemodialysis.

Case report

A woman in her 40s, with no cardiovascular history or family history of heart disease, affected by polycystic kidney disease (PKD) and end-stage CKD placed on haemodialysis for the previous 9 months, underwent a transthoracic echocardiography (TTE) in September 2021, as part of preparatory investigations for possible kidney transplantation. The TTE showed a picture consistent with dilated cardiomyopathy (DCM) with reduced EF (*Figure 1*; *Videos S1 and S2*), severe left atrium (LA) dilation and moderate-to-severe mitral regurgitation (MR). Thus, the patient was temporarily suspended from the transplant list to perform further investigations. She led an active life, practicing mild aerobic sports activity twice to 3 times a week at the gym, and was symptomatic for occasional episodes of exertional dyspnoea (NYHA functional classes I–II). She had never had cardiological investigations in the past, and she was on therapy for hypertension with enalapril 20 mg o.d. and doxazosin 4 mg o.d. with good control of blood pressure values. She was on chronic diuretic therapy with high dose of furosemide (250 mg b.i.d.), with a residual diuresis of 400–500 mL per day.

She was admitted to our hospital for an elective coronary angiography (CA), which showed normal coronary arteries, and then discharged after 24 h to allow for the next dialysis session. In the same week, she underwent a cardiac magnetic resonance (CMR) without contrast administration (gadolinium) due to severe CKD, which confirmed the diagnosis of DCM with severe dilation of the left ventricle (LV), reduced EF, and severe MR (*Figure 2*, *Videos S3–S5*). Interestingly, both the native T1 and T2 mapping were within the normal range, excluding significant myocardial tissue alteration (*Figure 2*). On the same day, a cardiopulmonary exercise test (CPET) was also performed showing a mild functional limitation with no signs of pulmonary vascular limitation. The main baseline clinical, TTE, CMR, CPET, and biochemical data are reported in *Table 1* (left side). After a multidisciplinary evaluation involving HF specialists and nephrologists, the pharmacological treatment was modified. In particular, doxazosin and enalapril were suspended, and the recommended quadruple HF therapy was started and gradually up-titrated during the following 10 months (*Figure 3*, upper panel). Importantly, neither the haemodialysis protocol nor the diuretic therapy was changed throughout this period (*Figure 3*, lower panel). Moreover, the patient's arteriovenous fistula was maintained as the vascular access for the dialytic treatment. The patient was informed of the off-label use of the new drug therapy, and she was closely monitored from both a cardiological and nephrological perspective. No adverse events were observed (e.g. need for increased sessions or dialysis schedule, hyperkalaemia, hypotension) (*Figure 3*, lower

Figure 1 2D and 3D echocardiographic data at baseline and at follow-up. Baseline echocardiographic data (upper panel) show a picture consistent with dilated cardiomyopathy with reduced EF, moderate MR, and severe LA dilatation. 2D and 3D echocardiography was performed again after 10 months (lower panel) showing a favourable reverse remodelling with MR reduction and normalization of both left chambers' dimensions and EF. 2D-LV, two-dimensional left ventricle; 3D-LV, three-dimensional left ventricle; EDV, end-diastolic volume; EF, ejection fraction; EROA, effective orifice regurgitant area; ESV, end-systolic volume; LA, left atrium; MR, mitral regurgitation; RV, regurgitant volume.

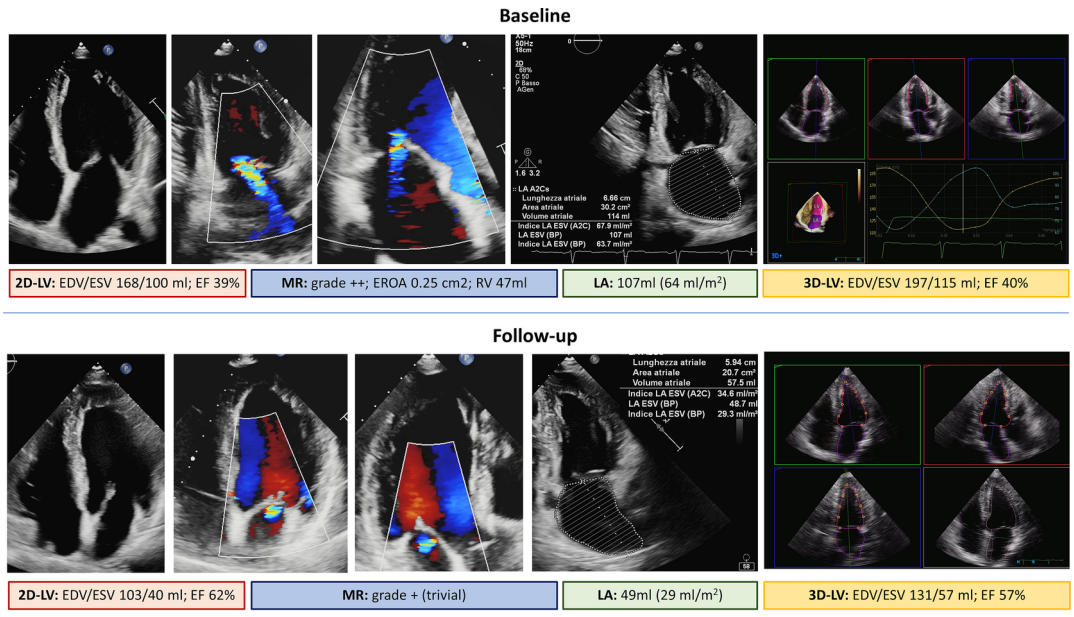
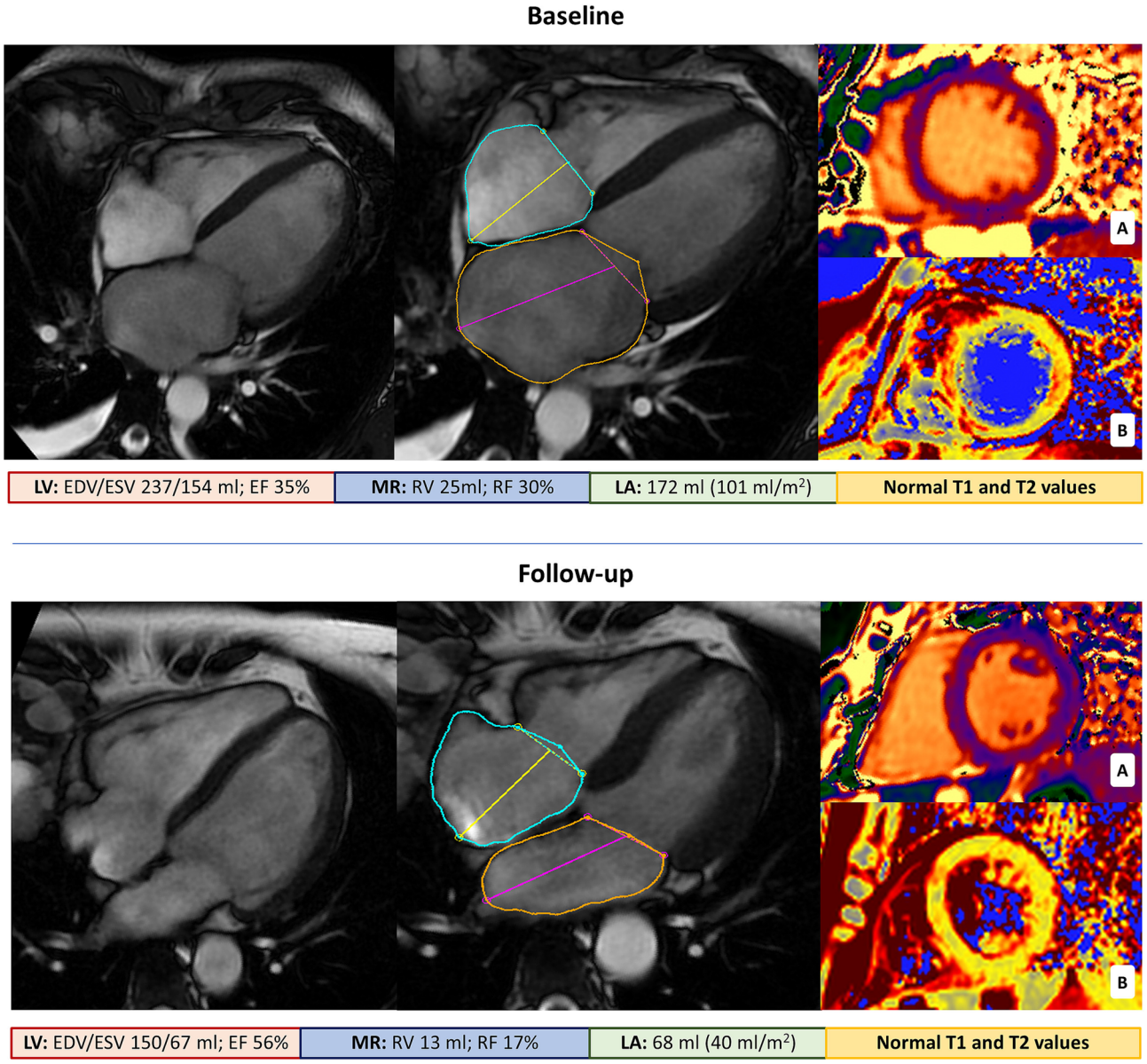


Figure 2 CMR data at baseline and at follow-up. Baseline CMR data (upper panel) show severe LV and LA dilatation. Panels A and B show normal values of T1 and T2 mapping, respectively. Follow-up CMR data (lower panel) show marked reverse modelling with the normalization of LV and LA volumes. Panels A and B show persistently normal values of T1 and T2 mapping, respectively. CMR, cardiac magnetic resonance; LA, left atrium; LV, left ventricle.



panel). During this timeframe, the patients was asymptomatic, and a progressive and sustained decrease in N-terminal pro B-type natriuretic peptide (NT-proBNP) from 26 356 to 1556 ng/mL was observed (*Figure 3*, upper panel). In parallel, we documented a significant amelioration in CPET and other laboratory parameters [including soluble suppression of tumorigenicity 2 (sST2)], as well as a consistent reverse remodelling of the left heart chambers and a significant reduction in MR grade, as evaluated at follow-up by TTE and CMR (*Figures 1 and 2*, respectively; *Videos S6–S10*). *Table 1* summarizes the main changes in clinical values. By improvement in LVEF, peak oxygen intake (peak VO_2), minute ventilation/carbon dioxide production (VE/VCO_2) slope, and laboratory values, we observed a reduction (from 6.16 to 0.62%) in the estimated risk of death, urgent cardiac transplantation, or left ventricle assist device implantation at

Table 1 changes in the main clinical, TTE, CMR, CPET, and biochemical data

	Baseline	1st follow-up (6–8 months)	2nd follow-up (10–12 months)	Difference from baseline(%)
TTE-EDV(mL)	168	100	103	−39
TTE-EDVi(mL/m^2)	100	60	62	−38
TTE-ESV(mL)	100	43	40	−60
TTE-ESVi(mL/m^2)	59	26	24	−59
TTE-EF(%)	39	57	62	+59
TTE-LAV(mL)	107	49	55	−49
TTE-LAVi(mL/m^2)	64	29	33	−48
TTE-3D EDV(mL)	197	148	131	−34
TTE-3D ESV(mL)	115	64	57	−50
TTE-3D-EF(%)	40	57	57	+43
CMR-EDV(mL)	237	154	150	−37
CMR-ESV(mL)	154	80	67	−56
CMR-EF(%)	35	48	56	+60
CMR-MR(+/+++)	+++	+	+	n/a
NT-proBNP(ng/mL)	26 356	2556	1566	−94
sST2 (ng/mL)	33.3	n/a	28.4	−15
peakVO_2 (mL/kg/min)	17.8	18.8	23.3	+31
Peak VO_2 (% pred)	69	73	89	+29
VE/VCO_2 slope	31.2	32.2	30.2	−3

CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LAV, left atrium volume; MR, mitral regurgitation; n/a, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide; sST2, soluble suppression of tumorigenesis-2; TTE, transthoracic echocardiography; VE/VCO_2, minute ventilation/carbon dioxide production; VO_2, oxygen intake.

2 years according to the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score, one of the most used and robust prognostic scores in HFrEF[11] (*Figure 4*). In October 2022, a pre-transplant nephrectomy was performed, and given the clinical, echocardiographic, and functional improvement, the patient was finally listed for renal transplantation.

Discussion

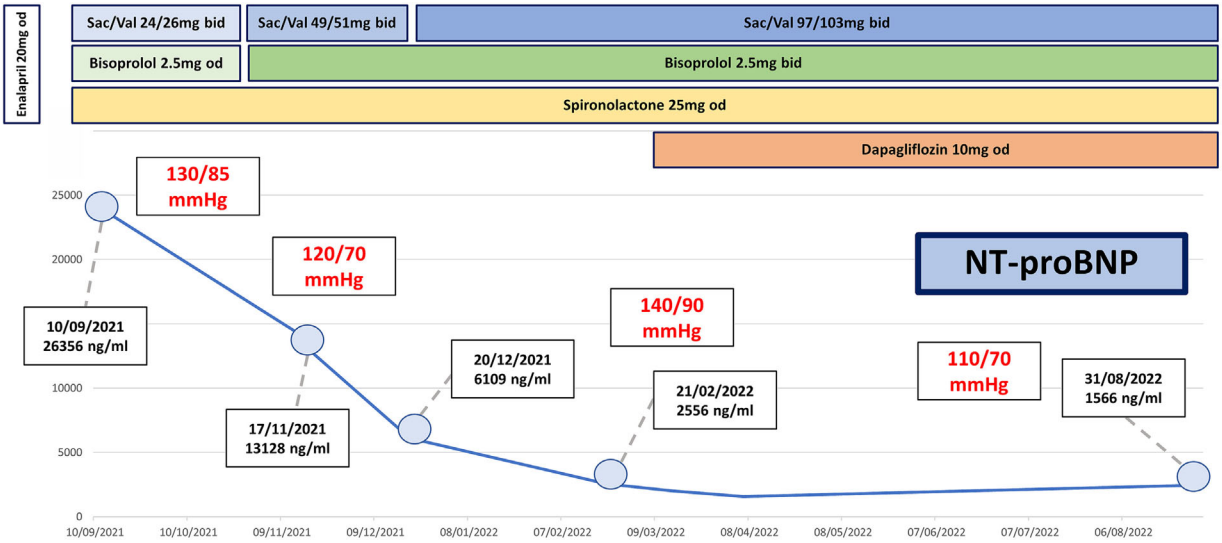
In this case report, we demonstrated how a comprehensive, high-dose anti-HF therapy may be effective in inducing a significant regression of the disease, even in complex patients such as those with end-stage CKD on haemodialysis. Changes in heart chamber dimensions, morphology, and function were documented with advanced and robust imaging techniques including 3DTTE, and CMR. Specifically, we observed a normalization of LV and LA volumes, functional capacity on CPET, and a 90% reduction in natriuretic peptide values. The effects of S/V therapy on LV remodelling and functional MR are well documented[12,13] both in ischaemic and non-ischemic DCM with a more favourable trend in the latter. S/V also demonstrated the capability to improve the 'HF syndrome' through multiple mechanisms, some more related to a predominant haemodynamic effect and others to pleiotropic effects.[14] Its impact on functional capacity (i.e. peak VO_2 and VE/VCO_2 slope) has been already described,[15] and it makes the drug's effect on those functional variables traditionally correlated with HF prognosis even more robust.

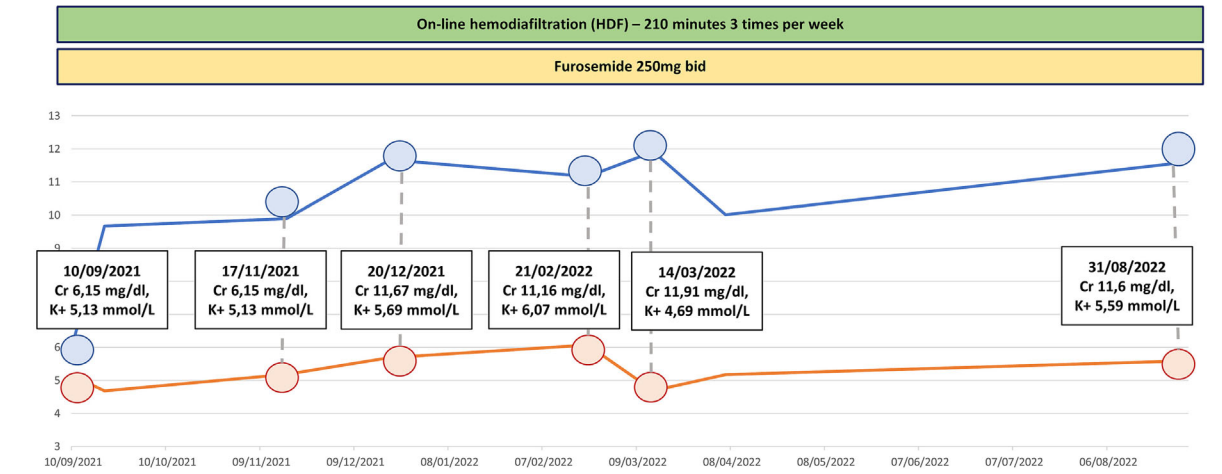
Although excluded from RCTs, some patients with end-stage CKD on dialysis have been favourably treated with S/V, both in HFrEF[16,17] and HFpEF.[18] In a retrospective trial by Lee et al., for example, 23 HFrEF patients on dialysis showed a significant reduction in sST2 (40.4 ± 44.0 to 19.6 ± 14.1 ng/mL; P = 0.005) together with an improvement in LVEF (from 29.7 ± 4.4% to 40.8 ± 10.4% (P = 0.002).

SGLT2i have recently been shown to be drugs with unique characteristics in terms of tolerability and prognostic effect on both cardiovascular and renal outcomes in HF patients.[6,9,19–22] Although these effects are consistent for all classes of baseline glomerular filtrate rates (including $<$30 mL/min/1.73 m^2),[23] the RCTs conducted in these patients excluded end-stage CKD. At present, while we await data from ongoing RCTs in patients on haemodialysis (NCT05179668), the use of SGLT2i in this setting can be derived only from observational data (i.e. patients enrolled in the DAPA-HF trial who started dialysis during the study follow-up and in whom SGLT2i treatment was not discontinued). In any case, SGLT2i have also demonstrated favourable effects on reverse cardiac remodelling, although, compared with S/V, the magnitude of this effect seems to be more related to cardiac mass than to LV volumes and EF,[24] suggesting that part of the favourable prognostic effect of these drugs can be extra-cardiac.

Our patient's dramatic reverse remodelling may depend on various more or less random factors including the

Figure 3 Patient's treatment timeline. The figure (upper panel) shows the trend of NT-proBNP and blood pressure values during the months of treatment (September 2021 to August 2022). HF disease-modifying drugs are shown at the top with their respective dosages. The lower panel shows the trend of serum potassium and creatinine during the same period. The dialysis schedule and the dosage of the loop diuretic remained stable throughout the follow-up. Cr, creatinine; HF, heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide; Sac/Val, sacubitril/valsartan.

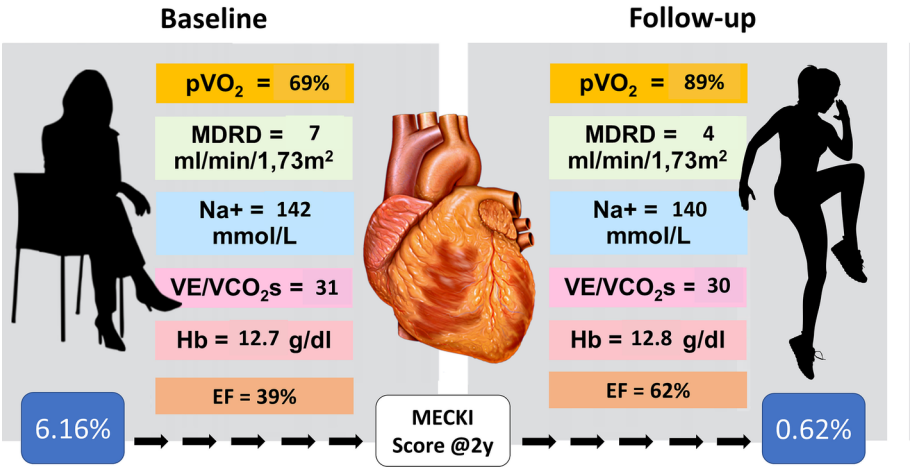




simultaneous use of multiple HF medications (at baseline she was receiving only ACE-I) and to the absence of significant alterations in tissue characterization at CMR, a possible expression of tissue scarring that is unlikely to regress with medical therapy. In contrast, this improvement appears to be completely independent of the patient's loading condition since the dialytic schedule, the diuretic regimen, and the presence of the arteriovenous fistula were all constant throughout observation. In addition, the diuretic effect of anti-HF drugs (S/V, SGLT2-i, and MRAs), which may play an important role in some subjects (e.g. diabetics on glycosuric therapy or patients with normal glomerular filtration rate), can hardly have played a determining role in a patient almost completely dependent on dialysis. Taken together, all these data seem to suggest that the ancillary (in other words, not simply diuretic) effects of new HF drugs are fundamental in reducing (or reversing) disease progression, provided they intervene early in the natural history of the syndrome. In this regard, our patient had never been hospitalized for HF and was leading a healthy, paucisymptomatic life before starting HF drugs.

We described a case of significant left heart chambers reverse remodelling and disease regression in a patient with end-stage CKD presenting with HFrEF and treated with opti-

Figure 4 Comparison of prognostic prediction between baseline and follow-up based on major clinical variables in HFrEF. The figure shows the changes in the six variables included in the MECKI prognostic score (11) for estimating cardiovascular mortality and/or urgent cardiac transplantation/LVAD implantation at 2 years. The score combines 1 echocardiographic, 2 CPET, and 3 laboratory data. The 2-year risk is reduced by about 10-fold (from 6.16 to 0.62%) with the changes induced by anti-HF therapy. CPET, cardiopulmonary exercise test; EF, ejection fraction; Hb, haemoglobin; HFrEF, heart failure with reduced ejection fraction; LVAD, left ventricular assist device; MDRD, Modification of Diet in Renal Disease; MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; pVO_2, peak oxygen intake (expressed as % of the predicted); VE/VCO_2s, minute ventilation/carbon dioxide production slope.



mized HF medical therapy. These hypothesis-generating data, suggesting a beneficial effect of the off-label use of the 'four pillars' also in the setting of haemodialysis, need to be confirmed in further studies before using strategies such as these extensively.

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Conflict of interest

The authors certify that they have no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Video S1. Baseline echocardiography showing dilated cardiomyopathy with reduced ejection fraction (4 chambers view).
Video S2. Baseline echocardiography showing mitral regurgitation (3 chambers view with color flow Doppler).
Video S3. Baseline cardiac magnetic resonance cine sequences showing dilated cardiomyopathy with reduced ejection fraction.
Video S4. *Baseline cardiac magnetic resonance cine sequences showing dilated cardiomyopathy with reduced ejection fraction.*
Video S5. Baseline cardiac magnetic resonance cine sequences showing dilated cardiomyopathy with reduced ejection fraction.
Video S6. Follow-up echocardiography showing normalization of left ventricle and left atrium dimensions and function (4 chambers view).
Video S7. *Follow-up echocardiography showing reduction of mitral regurgitation from moderate/severe to trivial (3 chambers view with color flow Doppler).*
Video S8. *Follow-up cardiac magnetic resonance cine sequences showing normalization of left ventricle and left atrium dimensions and function.*

Video S9. *Follow-up cardiac magnetic resonance cine sequences showing normalization of left ventricle and left atrium dimensions and function.*

Video S10. Follow-up cardiac magnetic resonance cine sequences showing normalization of left ventricle and left atrium dimensions and function.

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