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ORIGINAL ARTICLE

Successful conservative management of left ventricular assist device candidates

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Abstract

Aims Clinical trials comparing LVADs vs. conservative therapy were performed before the availability of novel medications or used suboptimal medical therapy. This study aimed to report that long-term stabilization of patients entering a left ventricular assist device (LVAD) programme is possible with the use of aggressive conservative therapy. This is important because the excellent clinical stabilization provided by LVADs comes at the expense of significant complications.

Methods and results This study was a single-centre prospective evaluation of consecutive patients with advanced heart failure (HF) fulfilling criteria for LVAD implantation based on clinical and echocardiographic characteristics, cardiopulmonary exercise test, and right heart catheterization results. Their initial therapy included inotropes, thiamine, beta-blockers, digoxin, spironolactone, hydralazine, and nitrates followed by the introduction of novel HF therapies. Coronary revascularization and cardiac resynchronization therapy were performed when indicated, and all patients were closely followed at our outpatient clinic. During the study period, 28 patients were considered suitable for LVAD implantation (mean age 63 ± 10.8 years, 92% men, 78% ischaemic, median HF duration 4 years). Clinical stabilization was achieved and maintained in 21 patients (median follow-up 20 months, range 9–38 months). Compared with baseline evaluation, cardiac index increased from 2.05 (1.73–2.28) to 2.88 (2.63–3.55) L/min/m^2, left ventricular end-diastolic diameter decreased from 65.5 (62.4–66) to 58.3 (53.8–62.5) mm, and maximal oxygen consumption increased from 10.1 (9.2–11.3) to 16.1 (15.3–19) mL/kg/min. Three patients died and only four ultimately required LVAD implantation.

Conclusions Notwithstanding the small size of our cohort, our results suggest that LVAD implantation could be safely deferred in the majority of LVAD candidates.

Keywords Advanced heart failure; LVAD; Drug therapy

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Introduction

Patients with advanced heart failure (HF) who are unresponsive or intolerant to optimal medical therapy (OMT) are nowadays offered implantation of a left ventricular assist device (LVAD), either as a bridge to a heart transplantation or as destination therapy.[1] However, the definitions of OMT and 'intolerance to OMT' are not always rigorous. In fact, a surprisingly high percentage of patients undergoing LVAD implantation in contemporaneous series receive suboptimal medical therapy. Furthermore, the only two randomized studies that compared LVAD implantation vs. OMT used medical therapy that would be considered outdated by present standards[2] or reported only the use of beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs).[3] This is important because the excellent clinical stabilization provided by LVAD implantation comes at the expense of significant LVAD-related complications.[4,5]

We report a prospective evaluation of consecutive patients with advanced HF who were referred for LVAD implantation at our centre, a tertiary hospital for advanced HF. We report that, when LVAD implantation was planned, the majority of

these patients were *not* receiving OMT. Furthermore, we report that the majority of patients referred for LVAD implantation could be managed conservatively with good medium-term results.

Methods

All consecutive patients with advanced HF who were referred to our centre for LVAD implantation between January 2018 and December 2020 were systematically evaluated. They all had severe left ventricular (LV) systolic dysfunction and severe HF and were either acutely admitted or referred to our centre by their treating cardiologist. Data were prospectively collected. The study was approved by our institutional review board (identifier: 0574-16-TLV; Clinical Trials registration number: NCT05271214).

All patients had advanced HF[6] and were considered candidates for LVAD implantation. As such, they underwent extensive cardiac evaluation. This included comprehensive echocardiography, right heart catheterization (RHC), and a cardiopulmonary exercise test. Based on this initial evaluation, patients were graded according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile. Individualized guideline-directed medical therapy was initiated[7] (see *Table 2* for a complete description). Following therapy optimization, evaluation was repeatedly performed during the next months in order to continuously re-evaluate the need for an LVAD implantation. Repeated evaluation included clinical assessment, laboratory testing, comprehensive echocardiography, and cardiopulmonary exercise test in all cases. Of note, echocardiography was used for repeated haemodynamics and repeated RHC was done on an individual basis.

Our therapeutic goal consisted of initial stabilization during the index admission. Our protocol included intravenous furosemide (as needed) and continuous intravenous milrinone of 0.25–0.5 mcg/kg/min. Intravenous thiamine (500–1500 mg) was generally added. Beta-blockers were continued or added within the first 24 h and were switched to HF-established beta-blockers within 48 h. Hydralazine was initiated within the first 48 h and nitrates were added after reaching 60 mg hydralazine per day. A loading dose of digoxin (i.e. total 1 mg) was given during the first 48 h, followed by low-dose oral digoxin with an aim of maintaining digoxin serum levels of 0.4–0.8 ng/mL. Investigation for iron deficiency and vitamin D levels was done within 24 h from admission and corrections were initiated early. Low-dose spironolactone was the first renin-angiotensin-aldosterone system (RAAS) inhibitor used, followed by low-dose valsartan with an aim to introduce sacubitril/valsartan shortly thereafter. We used type-2 sodium-glucose transporter inhibitors (SGLT2i) during the index admission with an aim of decreasing diuretic doses and reaching early stabilization.[8] Coronary angiography was routinely done and revascularization interventions were considered on an individual basis. Cardiac resynchronization therapy (CRT) was used when appropriate.[7] After discharge, close follow-up, at intervals of 3–14 days, was performed at our outpatient HF clinic, including clinical evaluation, laboratory testing, and repeated cardiac imaging. Patients usually received intravenous diuretics and inotropes (levosimendan or milrinone). Drug up-titration was rigorously pursued (*Figure 1*).

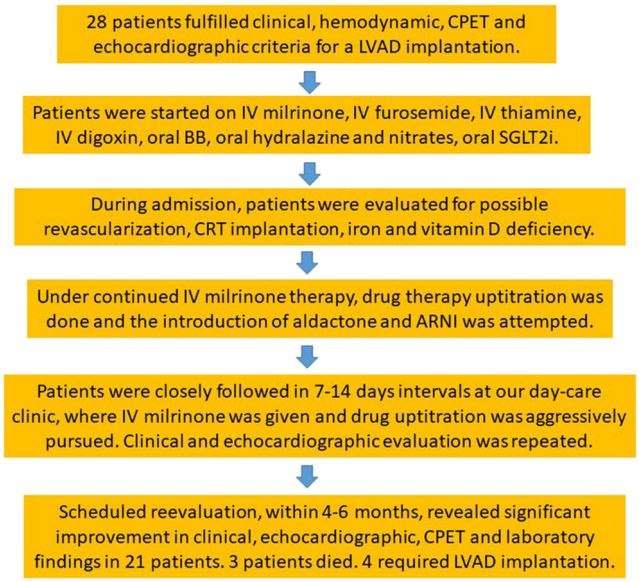
Cardiopulmonary exercise test

Beta-blocker therapy was neither changed nor modified for the test. Symptom-limited graded ramp exercise tests were performed with the use of either bicycle ergometer (Ergoline, 100P) or treadmill ergometer (Ram, 770CE). The work-rate increment protocol was tailored to the individual to yield fatigue-limited exercise duration of ~8 to 12 min. The protocol included 2 min of unloaded phase, a symptom-limited ramp graded exercise, and 2 min of recovery. Breath-by-breath minute tidal volume (TV), respiratory rate, VE, VCO_2, and VO_2 were measured using a Medical Graphics Metabolic Cart (Cortex, Metalyzer 3B). Peak VO_2 was the highest averaged 30 s VO_2 during exercise. Anaerobic threshold was determined manually using the modified V-slope method. VE/VCO_2 slope was calculated by linear regression with all exercise data obtained from the progressive exercise test. The metabolic–chronotropic relationship was calculated from the ratio of the heart rate (HR) reserve to the metabolic reserve during submaximal exercise. A metabolic–chronotropic relationship slope $<$ 0.80 was considered indicative of chronotropic incompetency. In patients receiving beta-blocker therapy, chronotropic incompetency was considered to be present when $<$62% of HR reserve was reached.

Echocardiography

Echocardiographic evaluation was performed in a standard manner, always using the same equipment (iE33, Philips Medical Systems, Bothell, WA). Left ventricular ejection fraction (LVEF) was calculated by Simpson's method. LV diameters, inter-ventricular septal diameter, and LV posterior wall width were measured during systole and diastole as recommended.[9] Forward stroke volume was calculated from LV outflow tract with subsequent calculation of cardiac output (CO). Left atrium volume was calculated using the biplane area length method at end systole. All volumetric measurements were adjusted to body surface area and reported as mL/m^2. Pulsed-wave Doppler was performed in the apical four-chamber view to obtain mitral inflow velocities to assess

Figure 1 With the use of intravenous milrinone, correction of thiamine, iron and vitamin D deficiencies, the introduction and up-titration of neurohormonal therapy, appropriate revascularization and cardiac resynchronization, and the ability to closely follow and treat advanced HF patients, the majority of LVAD candidates showed a significant subjective and objective improvement. ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; CPET, cardiopulmonary exercise test; CRT, cardiac resynchronization therapy; IV, intravenous; LVAD, left ventricular assist device; SGLT2i, type-2 sodium-glucose transporter inhibitors.



LV filling. Recordings were averaged over 3 and ≥7 consecutive cardiac cycles during sinus rhythm and atrial fibrillation, respectively. Measurements of mitral inflow included the peak early filling (E wave) and late diastolic filling (A wave) velocities, the E/A ratio, and deceleration time (DT) of early filling velocity. Early diastolic mitral annular velocities (e') were measured in the apical four-chamber view. The e' was measured from septal and lateral annulus in all studies. The ratio of peak E to peak e' (septal, lateral, and average) was calculated (mitral E/e' ratio) from the average of at least 3 cardiac cycles.[10] Apart from qualitative grading, right ventricular function was evaluated using S' and tricuspid annular plane systolic excursion (TAPSE). Haemodynamic assessment estimated tricuspid regurgitation velocity and right atrial pressure using the inferior vena cava to calculate the systolic pulmonary artery pressure.

Right heart catheterization

The catheterization was performed through a 7F sheath via the right internal jugular or right femoral vein. Pressures in the right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge position were measured at end expiration (mean of ≥3 beats) using fluid-filled manometer. Mean pressures were calibrated at the beginning of each case to avoid baseline drift. Transducers were zeroed at midaxillary level in each patient. Pressure tracings from the entire study were stored for offline analysis. Mean right atrium and pulmonary capillary wedge pressure (PCWP) were taken at mid-A wave. PCWP position was verified by typical waveforms, appearance on fluoroscopy, and, when needed, direct oximetry (PCWP blood saturation ≥ 94%). Arterial blood pressure was measured noninvasively. Arterial–venous O_2 content difference (AVo2diff) was measured directly as the difference between systemic arterial and Pao2 content (= saturation × haemoglobin × 1.34). Oxygen consumption (Vo2) was measured from expired gas analysis to calculate CO, by the direct Fick method (CO = Vo2 ÷ AVo2diff).

Statistical analysis

Distribution of continuous variables was assessed with the Shapiro–Wilk test. Mean (± standard deviation) or median [interquartile range (IQR) 25–75%] was reported depending on the distribution. Accordingly, differences between study groups were evaluated with the independent samples *t*-test or the Mann–Whitney *U* test. Categorical variables are described as absolute number (and percentage). Differences between groups were evaluated with Fisher's exact test. Diastolic dysfunction grades were compared using the Cochran–Armitage test. A two-tailed *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using R Version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 37 patients were referred for LVAD implantation, of whom 3 were referred by us to a nearby heart transplantation centre and 6 were excluded according to accepted criteria[4,5] (*Figure 2*). Thus, the study cohort consisted of 28 patients suitable for LVAD implantation, 26 men and 2 women, mean age 63 ± 10.8 years. The main aetiology (78%) was coronary heart disease (*Table 1*). At the time of referral, 16 and 12 patients were in Functional Class III or IV, respectively, and all patients had LVEF < 30% (*Table 1*). Eight patients required continuous inotropes (INTERMACS profile 3) when first considered for LVAD implantation. The rest suffered from a low CO state with peripheral hypoperfusion (including borderline blood pressure and kidney dysfunction) (INTERMACS profile 4–6). Baseline evaluation showed findings diagnostic of advanced HF in all patients. Their median [IQR] LVEF was 20% (16–24)%, left ventricular end-diastolic diameter (LVEDD) 65.5 (62.4–66) mm, cardiac index (CI) 2.05 (1.73–2.28) L/min/m^2, PCWP 24 (20–30) mmHg, and VO_2 max 10.1 (9.2–11.3) mL/kg/min (*Table 1*).

Before intervention, only eight (28%) patients were receiving all three guideline-recommended HF therapies[7] (excluding sodium-glucose transporter inhibitors, which were not recommended at the time of our study initiation) (*Table 2*). Five patients required coronary revascularization (surgical in one and percutaneous in four). Four patients underwent cardiac resynchronization therapy and defibrillator (CRTD) implantation and one underwent pulmonary vein isolation (*Table 2*). Following intervention, four patients, with compatible baseline characteristics (*Table 1*), still required LVAD implantation due to intractable HF symptoms (n = 3) or recurrent ventricular tachycardia (n = 1). One of the LVAD-implanted patients died 48 h after the procedure due to multi-organ failure, one developed an intracranial haemorrhage 8 months after device implantation (resolved without intervention), and two suffered from recurrent driveline infections.

Of the 24 patients who were referred for LVAD implantation but were treated conservatively, one died suddenly at home (3 weeks following initial evaluation; the patient was not implanted with a cardioverter defibrillator), one died from a septic shock after 4 months, and a third died after 14 months due to acute decompensation, which included severe kidney and right ventricular dysfunction. The rest of the cohort (n = 21) completed the intervention period with a median follow-up of 20 months (range 9–38 months). Scheduled re-evaluation (within 4–6 months) showed an overall improvement in all parameters. Specifically, CI increased from 2.05 (1.73–2.28) to 2.88 (2.63–3.55) L/min/m^2, LVEDD decreased from 65.5 (62.4–66) to 58.3 (53.8–62.5) mm, maximal oxygen consumption increased from 10.1 (9.2–11.3) to 16.1 (15.3–19) mL/kg/min, and brain natriuretic peptide levels decreased from 2795 (1628–4585) to 657 (283–852) pg/mL (*Figures 3–5*). The number of hospitalizations during the 12 months before and after the intervention was 3 [3–3] and 3.3 [3–4] in the LVAD-implanted group compared with 2.6 [2–4] and 1 [0–2] in those in whom LVAD implantation was deferred. Total admission days in the 12 months before and after intervention were 42, 27, 41 and 25, 55, 117 vs. 9 (0–41) and 7 (0–52) in patients who did or did not undergo LVAD implantation, respectively (*Table 3*).

Figure 2 Of 37 patients with clinical, laboratory, echocardiographic, and haemodynamic findings compatible with severe heart failure, 9 were excluded due to various reasons, leaving 28 patients who were aggressively treated. Of these patients, 3 died and only 4 eventually required a left ventricular assist device implantation. HTx, heart transplantation; LVAD, left ventricular assist device; PVD, peripheral vascular disease.

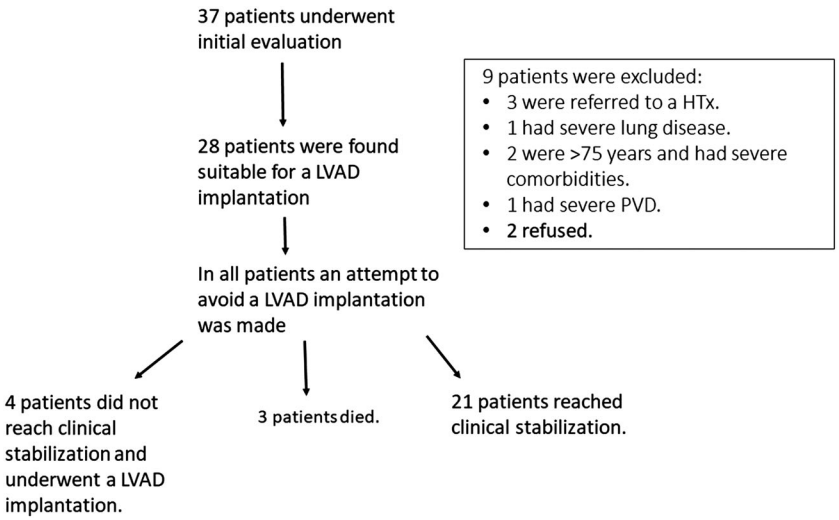


Table 1 Baseline characteristics

	No LVAD (n = 24)	LVAD (n = 4)	P value
Age (years), mean ± SD	63 ± 7	63 ± 11	0.95
Gender (male), *n* (%)	22 (92)	4 (100)	0.99
Ischaemic aetiology, *n* (%)	18 (75)	4 (100)	0.55
Duration of HF (years), median (IQR)	4 (3–5)	7 (4.5–8)	0.01
SBP (mmHg), mean ± SD	99 ± 9	102 ± 15	0.56
Haemoglobin (g/dL), mean ± SD	13.2 ± 1.6	13.3 ± 3	0.91
Creatinine (mg/dL), mean ± SD	1.4 ± 0.3	1.7 ± 0.8	0.54
eGFR (mL/min), median (IQR)	63 (40–72)	54 (32–77)	0.87
BNP (pg/mL), median (IQR)	2805 (1607–5000)	1716 (464–4452)	0.39
ICD/CRTD, *n* (%)	18 (75)	4 (100)	0.55
VO_2 max (mL/kg/min), mean ± SD	10.2 ± 1.7	11.1 ± 3.2	0.61
VE/VCO_2, mean ± SD	42.7 ± 5.7	39.0 ± 7.3	0.26
LVEDD (mm), median (IQR)	66 (62–66)	62 (60–67)	0.59
LVEF (%), median (IQR)	20 (15–25)	28 (21–30)	0.08
CO (L/min), mean ± SD	2.8 ± 0.4	3.1 ± 0.4	0.16
PCWP (mmHg), median (IQR)	26 (19–30)	24 (19–29)	0.87
ACEI/ARB/ARNI, *n* (%)	16 (67)	3 (75)	0.99
BB, *n* (%)	15 (63)	4 (100)	0.27
MRA, *n* (%)	11 (46)	3 (75)	0.59
Furosemide dose (mg), median (IQR)	120 (55–160)	80 (80–160)	0.52
NYHA class, *n* (%)			0.99
III	14 (58)	2 (50)	
IV	10 (42)	2 (50)	
INTERMACS profile ≤ 4	15 (63)	4 (100)	0.27

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; BNP, brain natriuretic peptide; CO, cardiac output; CRTD, cardiac resynchronization therapy and defibrillator; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IQR, interquartile range; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor blocker; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; SD, standard deviation; VE/VCO_2, the ratio of ventilation to CO_2 production; VO_2 max, maximal oxygen consumption.

Discussion

In this prospective cohort, 75% of patients who were referred for LVAD implantation because of 'drug refractory, intractable HF' and entered our LVAD programme could be treated conservatively with good medium-term results. With careful utilization of inotropes, graded optimization of neurohormonal therapy, and appropriate use of coronary revascularization and CRT, most of our LVAD candidates reached clinical stabilization without the use of LVADs. Our integrated approach enabled our patients to achieve an improvement in peak oxygen consumption compatible with the one shown after an LVAD implantation.[11] The ability to closely monitor and treat ambulatory patients was instrumental for preserving good results with conservative therapy.

The world of HF is quickly evolving and new therapeutic approaches allow us to profoundly assist patients who, until recently, were considered to have 'end-stage HF'. Regrettably, data show that despite their dire need, too many advanced HF patients are deprived of appropriate neurohormonal therapy, consequently exposing them to rapid deterioration.[12]

LVAD implantation offers remarkable improvement in tissue perfusion but at the expense of significant complications. In the Multicenter Study of Magnetically Levitated Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) study, within only 6 months of LVAD therapy, 8% of patients implanted with centrifugal pump had experienced stroke, 10% had experienced bleeding requiring surgery, and 12% had driveline infection; the risk of all these complications was even higher for patients implanted with axial pumps (11% and 14% for stroke and bleeding, respectively).[4] Also, the 6 month mortality rate for LVAD-implanted patients was 9%.[4] Similar complication rates were reported with the HeartWare device.[5] Clearly, although LVADs significantly improve HF patients' symptomatology and outcomes, their potential side effects are so severe that alternative therapeutic options should be initially exhausted.

Regrettably, medical therapy of LVAD candidates in contemporaneous LVAD series is clearly *not* optimal (*Table 4*). Furthermore, there are only two randomized studies comparing LVAD implantation vs. conservative therapy. The first was the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH), which compared pulsatile LVADs vs. OMT in advanced HF patients who were ineligible for heart transplantation. This study showed 12 month survival benefit in LVAD-implanted patients. However, as it was conducted between 1998 and 2001, medical therapy included spironolactone in only 39%, ACEIs/angiotensin II receptor blockers (ARBs) in 69%, and beta-blockers in 20% of the patients.[2] The second, more con-

Table 2 Treatment before and after intervention

Patient number	Before intervention	Initiated therapy[a]	Maintenance therapy
#1	Carvedilol 6.25 mg bid, ramipril 2.5 mg od, spironolactone 25 mg od, furosemide 80 mg bid.	IV milrinone 0.375 mcg/kg/min, IV furosemide 125 mg/day, stop carvedilol, stop ramipril, IV iron sucrose 600 mg, bisoprolol 5 mg bid, sacubitril/valsartan 100 mg bid, spironolactone 25 mg bid, empagliflozin 5 mg od, cholecalciferol 2000 IU bid.	Intermittent twice weekly IV milrinone 0.5 mcg/kg/min (stopped after 3 months), bisoprolol 5 mg bid, sacubitril/valsartan 200 mg bid, eplerenone 25 mg bid, furosemide 40 mg bid, empagliflozin 10 mg od, cholecalciferol 1000 IU bid, hydralazine 30 mg tid, ISMN 20 mg bid, coenzyme Q10 300 mg od.
#2	Metoprolol tartrate 50 mg bid, rami pril 5 mg od, furosemide 40 mg bid.	IV milrinone 0.375 mcg/kg/min, stop metoprolol, stop ramipril, IV iron sucrose 600 mg, digoxin 1 mg, bisoprolol 2.5 mg bid, sacubitril/valsartan 100 mg bid, spironolactone 25 mg od, CRTD.	Intermittent twice weekly IV milrinone 0.5 mcg/kg/min (reduced to once weekly after 3 months), bisoprolol 5 mg bid, sacubitril/valsartan 200 mg bid, spironolactone 25 mg bid, furosemide 40 mg bid, digoxin 0.125 mg 5 times weekly, hydralazine 30 mg tid, ISMN 10 mg bid, CRTD.
#3	Bisoprolol 5 mg od, ramipril 2.5 mg od, spironolactone 12.5 mg od, furosemide 60 mg od.	IV milrinone 0.375 mcg/kg/min, IV furosemide 250 mg/day, IV thiamine 1000 mg, IV iron sucrose 600 mg, bisoprolol 5 mg bid, stop ramipril, sacubitril/valsartan 50 mg bid, spironolactone 25 mg od, empagliflozin 5 mg od, cholecalciferol 2000 IU bid.	Bisoprolol 5 mg bid, sacubitril/valsartan 200 mg bid, spironolactone 25 mg bid, furosemide 20 mg bid, empagliflozin 10 mg od, cholecalciferol 1000 IU bid, hydralazine 30 mg tid, ISMN 20 mg bid, coenzyme Q10 300 mg od.
#4	Furosemide 120 mg daily.	IV milrinone 0.5 mcg/kg/min, IV thiamine 500 mg, IV furosemide 125 mg/day, IV iron sucrose 600 mg, bisoprolol 1.25 mg bid, IV digoxin 1 mg, hydralazine 10 mg tid, spironolactone 25 mg od, sacubitril/ valsartan 50 mg od, cholecalciferol 2000 IU bid, PCI to LAD.	Bisoprolol 3.75 mg bid, sacubitril/ valsartan 200 mg bid, eplerenone 25 mg bid, patiromer 16.8 g od, digoxin 0.125 mg 5 times weekly, hydralazine 20 mg tid, ISMN 10 mg bid, cholecalciferol 1000 IU bid, coenzyme Q10 300 mg od, empagliflozin 12.5 mg od.
#5	Bisoprolol 2.5 mg od, losartan 25 mg od, furosemide 80 mg tid.	IV milrinone 0.5 mcg/kg/min, IV thiamine 500 mg, IV furosemide 500 mg/day, IV dopamine 3 mg/kg/min for 72 h, intermittent metolazone 5 mg, IV iron sucrose 1000 mg, bisoprolol 2.5 mg bid, IV digoxin 1 mg, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/ valsartan 50 mg od, cholecalciferol 2000 IU bid, CRTD implantation.	Intermittent twice weekly IV milrinone 0.5 mcg/kg/min (stopped after 3 months), bisoprolol 5 mg bid, sacubitril/valsartan 150 mg bid, spironolactone 25 mg bid, furosemide 80 mg + 40 mg/day, digoxin 0.125 mg 3 times weekly, hydralazine 20 mg tid, ISMN 10 mg bid, cholecalciferol 1000 IU bid, CRTD, PVI.
#6	Carvedilol 6.25 mg bid, enalapril 2.5 od, spironolactone 12.5 mg od, furosemide 80 mg bid.	Stop carvedilol, stop enalapril, IV milrinone 0.375 mcg/kg/min, IV thiamine 500 mg, IV furosemide 500 mg/day, IV dopamine 3 mg/kg/min for 72 h, intermittent metolazone 5 mg, IV iron sucrose 1000 mg, bisoprolol 2.5 mg bid, spironolactone 25 mg bid, sacubitril/ valsartan 50 mg bid, cholecalciferol 2000 IU bid.	Intermittent once weekly IV levosimendan 0.1 mcg/kg/min, intermittent once weekly IV furosemide 100 mg, bisoprolol 5 mg bid, sacubitril/ valsartan 200 mg bid, spironolactone 25 mg bid, furosemide 40 mg bid, cholecalciferol 1000 IU bid, coenzyme Q10 300 mg od.
#7	Metoprolol 25 mg bid, furosemide 80 mg daily.	IV milrinone 0.25 mcg/kg/min, IV furosemide 250 mg/day, bisoprolol 2.5 mg/day, spironolactone 12.5 mg/day, hydralazine 10 mg tid.	Intermittent once weekly IV milrinone 0.25 mcg/kg/min and IV furosemide 100 mg (both stopped after 3 months), bisoprolol 5 mg bid, sacubitril/valsartan 200 mg bid, spironolactone 25 mg od, dapagliflozin 10 mg od, furosemide 20 mg bid, cholecalciferol 1000 IU bid, PCI to LCX.
#8	Bisoprolol 1.25 od, candesartan 4 mg bid, furosemide 80 mg bid.	IV milrinone 0.25 mcg/kg/min, IV thiamine 1500 mg, IV furosemide 500 mg/day, IV dopamine 3 mg/kg/min for 72 h, intermittent metolazone 5 mg, IV iron sucrose 1000 mg, bisoprolol 2.5 mg bid, IV digoxin 1 mg, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg bid.	The patient died 14 months following initial evaluation and therapy due to acute heart failure complicated by severe kidney and right ventricular dysfunction.

(*Continues*)

Table 2 (continued)

Patient number	Before intervention	Initiated therapy[a]	Maintenance therapy
#9	Metoprolol tartrate 50 mg bid, ramipril 5 mg od, furosemide 40 mg tid.	IV milrinone 0.375 mcg/kg/min, IV furosemide 125 mg/day, IV digoxin 1 mg, stop metoprolol, stop ramipril, bisoprolol 2.5 mg bid, sacubitril/valsartan 50 mg bid, spironolactone 25 mg od, empagliflozin 5 mg od, hydralazine 10 mg tid, ISMN 10 mg bid, cholecalciferol 2000 IU bid.	Bisoprolol 5 mg bid, sacubitril/valsartan 200 mg bid, spironolactone 25 mg bid, furosemide 20 mg bid, empagliflozin 10 mg od, digoxin 0.125 mg 5 times weekly, hydralazine 30 mg tid, ISMN 20 mg bid, cholecalciferol 1000 IU bid.
#10	None.	IV milrinone 0.5 mcg/kg/min, IV thiamine 500 mg, IV furosemide 125 mg/day, IV iron sucrose 600 mg, IV digoxin 1 mg, bisoprolol 1.25 mg bid, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	Intermittent twice weekly IV milrinone 0.5 mcg/kg/min (stopped after 3 months), bisoprolol 5 mg bid, sacubitril/valsartan 200 mg bid, spironolactone 25 mg bid, patiromer 16.8 g od, furosemide 20 mg bid, digoxin 0.125 mg 5 times weekly, hydralazine 30 mg tid, ISMN 20 mg bid, cholecalciferol 1000 IU bid, empagliflozin 10 mg od, coenzyme Q10 300 mg od.
#11	Bisoprolol 2.5 mg od, spironolactone 12.5 mg od, furosemide 80 mg tid, metolazone 5 mg once weekly.	IV milrinone 0.5 mcg/kg/min, IV thiamine 1000 mg, IV furosemide 500 mg/day, IV dopamine 3 mg/kg/min for 72 h, intermittent metolazone 5 mg, IV iron sucrose 600 mg, bisoprolol 2.5 mg bid, IV digoxin 1 mg, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	The patient underwent an LVAD implantation after clinical deterioration due to repeated SMVT events.
#12	Bisoprolol 2.5 mg od, valsartan 40 mg od, furosemide 80 mg tid.	IV milrinone 0.5 mcg/kg/min, IV furosemide 500 mg/day, IV dopamine 3 mg/kg/min, intermittent metolazone 5 mg, IV iron sucrose 600 mg, bisoprolol 2.5 mg bid, digoxin 0.125 mg 5 times weekly, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg od. cholecalciferol 2000 IU bid.	The patient underwent an LVAD implantation due to refractory HF symptoms.
#13	Bisoprolol 2.5 mg od, furosemide 80 mg tid.	IV milrinone 0.375 mcg/kg/min, IV thiamine 500 mg, IV furosemide 500 mg/day, intermittent metolazone 5 mg, IV iron sucrose 1000 mg, bisoprolol 2.5 mg bid, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	Intermittent twice weekly IV milrinone 0.5 mcg/kg/min (reduced to once weekly after 3 months), intermittent once weekly IV furosemide 100 mg, bisoprolol 5 mg bid, sacubitril/valsartan 50 mg bid, spironolactone 25 mg od, hydralazine 30 mg tid, ISMN 10 mg bid, furosemide 40 mg tid, cholecalciferol 1000 IU bid, CRTD.
#14	Atenolol 25 mg bid, losartan 25 od, furosemide 40 mg bid.	IV milrinone 0.375 mcg/kg/min, IV furosemide 250 mg/day, IV iron sucrose 600 mg, digoxin 1 mg, stop atenolol, stop losartan, bisoprolol 1.25 mg bid, hydralazine 10 mg tid, ISMN 10 mg bid.	Intermittent twice weekly IV milrinone 0.5 mcg/kg/min (reduced to once weekly after 3 months), intermittent once weekly IV furosemide 100 mg, bisoprolol 2.5 mg bid, spironolactone 25 mg bid, empagliflozin 10 mg od, hydralazine 50 mg tid, ISMN 20 mg bid, furosemide 40 mg tid, digoxin 0.125 mg 4 times weekly, coenzyme Q10 300 mg od, PCI to LAD.
#15	Bisoprolol 5 mg bid, losartan 25 mg od, furosemide 80 mg bid.	IV milrinone 0.375 mcg/kg/min, IV furosemide 250 mg/day, IV iron sucrose 600 mg, bisoprolol 5 mg bid, sacubitril/valsartan 50 mg bid, empagliflozin 5 mg od, cholecalciferol 1000 IU bid.	The patient underwent an LVAD implantation due to refractory HF symptoms.

(*Continues*)

Table 2 (continued)

Patient number	Before intervention	Initiated therapy[a]	Maintenance therapy
#16	Metoprolol succinate 100 mg od, ramipril 5 mg od, furosemide 80 mg bid.	IV milrinone 0.375 mcg/kg/min, IV thiamine 500 mg, IV furosemide 500 mg/day, intermittent metolazone 5 mg, IV iron sucrose 1000 mg, metoprolol succinate 100 mg od, spironolactone 12.5 mg od, stop ramipril, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid, PCI to LAD.	Intermittent once weekly IV milrinone 0.25 mcg/kg/min and IV furosemide 100 mg (both stopped after 3 months), metoprolol succinate 75 mg bid, sacubitril/valsartan 200 mg bid, spironolactone 25 mg od, patiromer 8.4 g od, furosemide 40 mg bid, cholecalciferol 1000 IU bid, dapagliflozin 10 mg od, PCI to MG.
#17	Carvedilol 12.5 + 6.25 mg, ramipril 2.5 od, spironolactone 12.5 mg od, furosemide 80 mg bid.	IV milrinone 0.5 mcg/kg/min, IV thiamine 500 mg, IV furosemide 80 mg/day, IV iron sucrose 600 mg, stop carvedilol, stop ramipril, bisoprolol 2.5 mg bid, spironolactone 25 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	The patient was found dead at his residence 3 weeks following initial evaluation and therapy.
#18	None.	IV milrinone 0.5 mcg/kg/min, IV thiamine 500 mg, IV furosemide 125 mg/day, IV iron sucrose 600 mg, bisoprolol 1.25 mg bid, IV digoxin 1 mg, hydralazine 10 mg tid, spironolactone 25 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	Intermittent twice weekly IV milrinone 0.5 mcg/kg/min (stopped after 3 months), bisoprolol 5 mg bid, sacubitril/valsartan 200 mg bid, spironolactone 25 mg bid, furosemide 40 mg bid, digoxin 0.125 mg 5 times weekly, hydralazine 20 mg tid, cholecalciferol 1000 IU bid.
#19	Bisoprolol 2.5 mg od, ramipril 1.25 mg od, furosemide 120 mg bid.	IV milrinone 0.5 mcg/kg/min, IV thiamine 1000 mg, IV furosemide 500 mg/day, intermittent metolazone 5 mg, IV iron sucrose 1000 mg, bisoprolol 2.5 mg bid, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	The patient died due to septic shock.
#20	Carvedilol 12.5 mg bid, spironolactone 12.5 mg od, furosemide 80 mg bid.	IV milrinone 0.375 mcg/kg/min, IV thiamine 500 mg, IV furosemide 250 mg/day, IV iron sucrose 1000 mg, stop carvedilol, bisoprolol 2.5 mg bid, hydralazine 10 mg tid, spironolactone 12.5 mg bid, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	Intermittent twice weekly IV milrinone 0.5 mcg/kg/min (reduced to once weekly after 3 months), intermittent once weekly IV furosemide 100 mg, bisoprolol 5 mg bid, sacubitril/valsartan 150 mg bid, spironolactone 25 mg bid, hydralazine 30 mg tid, ISMN 10 mg bid, furosemide 40 mg tid, cholecalciferol 1000 IU bid, dapagliflozin 10 mg od.
#21	Bisoprolol 5 mg bid, sacubitril/valsartan 50 mg bid, spironolactone 25 mg od, furosemide 80 mg bid.	IV milrinone 0.5 mcg/kg/min, IV furosemide 250 mg/day, metolazone 5 mg once weekly, bisoprolol 2.5 mg bid, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	The patient underwent an LVAD implantation due to refractory HF symptoms but died 48 h after the implantation due to multi-organ failure.
#22	Bisoprolol 2.5 mg od, ramipril 3.75 mg od, spironolactone 12.5/48 h, furosemide 80 mg od.	IV milrinone 0.375 mcg/kg/min, IV thiamine 500 mg, IV furosemide 500 mg/day, intermittent metolazone 5 mg, IV iron sucrose 1000 mg, bisoprolol 2.5 mg bid, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	Intermittent once weekly IV levosimendan 0.1 mcg/kg/min, intermittent once weekly IV furosemide 100 mg, bisoprolol 2.5 mg bid, spironolactone 25 mg od, empagliflozin 10 mg od, hydralazine 50 mg tid, ISMN 20 mg bid, furosemide 40 mg od, digoxin 0.125 mg 2 times weekly, coenzyme Q10 300 mg od, cholecalciferol 1000 IU bid.
#23	Carvedilol 12.5 mg bid, ramipril 5 mg od, furosemide 80 mg bid.	IV milrinone 0.375 mcg/kg/min, IV thiamine 500 mg, IV furosemide 500 mg/day, intermittent metolazone 5 mg, IV iron sucrose 1000 mg, carvedilol 25 mg bid, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid.	Intermittent once weekly IV milrinone 0.5 mcg/kg/min (stopped after 3 months), intermittent once weekly IV furosemide 100 mg, carvedilol 25 mg bid, spironolactone 25 mg bid, empagliflozin 10 mg od, hydralazine 30 mg tid, ISMN 10 mg bid, furosemide 40 mg bid, digoxin 0.125 mg 4 times weekly, coenzyme Q10 300 mg od.

(*Continues*)

Table 2 (continued)

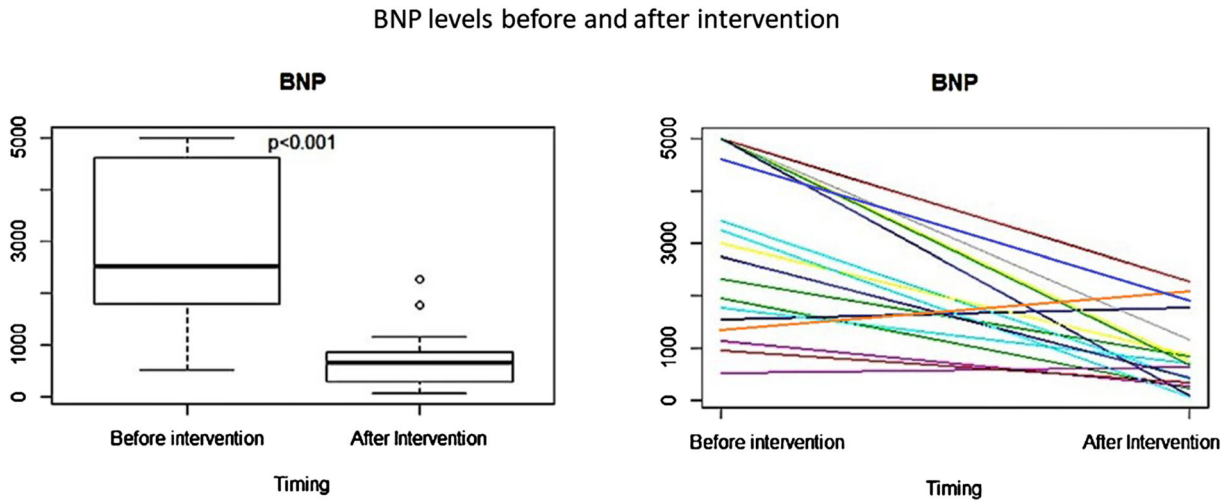
Patient number	Before intervention	Initiated therapy[a]	Maintenance therapy
#24	None.	IV milrinone 0.5 mcg/kg/min, IV thiamine 500 mg, IV furosemide 125 mg/day, IV iron sucrose 1000 mg, bisoprolol 2.5 mg bid, hydralazine 10 mg tid, spironolactone 12.5 mg od, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid. The patient underwent a CABG surgery.	Bisoprolol 7.5 mg od, sacubitril/valsartan 200 mg bid, spironolactone 25 mg bid, empagliflozin 10 mg od, cholecalciferol 1000 IU bid.
#25	Losartan 25 mg bid, furosemide 120 mg daily.	IV milrinone 0.25 mcg/kg/min, IV furosemide 375 mg/day, thiamine 1000 mg, stop metoprolol, bisoprolol 2.5 mg/day, spironolactone 12.5 mg/day, hydralazine 10 mg tid, digoxin 1 mg.	Intermittent once weekly IV milrinone 0.25 mcg/kg/min and IV furosemide 100 mg (both stopped after 3 months), bisoprolol 5 mg bid, sacubitril/valsartan 300 mg bid, spironolactone 25 mg od, dapagliflozin 10 mg od, furosemide 40 mg bid, cholecalciferol 1000 IU bid, PCI to LCX.
#26	Metoprolol tartrate 50 mg od, ramipril 1.25 mg od, furosemide 40 mg tid.	IV milrinone 0.375 mcg/kg/min, IV furosemide 250 mg/day, IV digoxin 1 mg, stop metoprolol, stop ramipril, bisoprolol 2.5 mg bid, sacubitril/valsartan 50 mg bid, spironolactone 25 mg od, empagliflozin 5 mg od, hydralazine 10 mg tid, ISMN 10 mg bid, cholecalciferol 2000 IU bid.	Bisoprolol 5 mg bid, sacubitril/valsartan 200 mg bid, spironolactone 25 mg bid, furosemide 20 mg bid, empagliflozin 10 mg od, digoxin 0.125 mg 3 times weekly, hydralazine 20 mg tid, ISMN 10 mg bid, cholecalciferol 1000 IU bid.
#27	Metoprolol succinate 50 mg od, ramipril 5 mg od, spironolactone 37.5 mg od, furosemide 60 mg bid, metolazone 2.5 mg once weekly.	IV milrinone 0.375 mcg/kg/min, IV thiamine 1000 mg, IV furosemide 500 mg/day, intermittent metolazone 5 mg, IV iron sucrose 600 mg, metoprolol succinate 100 mg od, spironolactone 25 mg bid, stop ramipril, sacubitril/valsartan 50 mg od, cholecalciferol 2000 IU bid, dapagliflozin 10 mg od.	Intermittent once weekly IV levosimendan 0.1 mcg/kg/min and IV furosemide 100 mg, metoprolol succinate 100 mg od, sacubitril/valsartan 150 mg bid, spironolactone 25 mg od, patiromer 8.4 g od, furosemide 40 mg bid, cholecalciferol 1000 IU bid, dapagliflozin 10 mg od.
#28	Bisoprolol 3.75 mg od, ramipril 2.5 mg bid, spironolactone 12.5 mg od, dapagliflozin 10 mg/48 h, furosemide 120 mg od.	IV milrinone 0.375 mcg/kg/min, IV furosemide 375 mg/day, IV thiamine 1000 mg, IV iron sucrose 600 mg, bisoprolol 5 mg od, stop ramipril, sacubitril/valsartan 50 mg bid, spironolactone 25 mg od, dapagliflozin 10 mg od.	Bisoprolol 5 mg bid, sacubitril/valsartan 200 mg bid, spironolactone 25 mg bid, furosemide 40 mg bid, empagliflozin 10 mg od, cholecalciferol 1000 IU bid, hydralazine 30 mg bid, ISMN 20 mg bid, coenzyme Q10 300 mg od.

CABG, coronary artery bypass graft; CRTD, cardiac resynchronization therapy and defibrillator; ISMN, isosorbide mononitrate; IV, intravenous; LAD, left anterior descending artery; LCX, left circumflex artery; LVAD, left ventricular assist device; MG, marginal artery; PCI, percutaneous coronary intervention; PVI, pulmonary vein isolation; SMVT, sustained monomorphic ventricular tachycardia.
[a]Intravenous therapy was initiated first, followed by a *gradual* introduction of oral therapy during hospital admission and at our outpatient day-care clinic.

temporary study, was the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management (ROADMAP) study, which compared axial flow LVAD vs. OMT in relatively stable advanced HF patients. The primary endpoint of the study (survival on original therapy) was reached by a higher proportion of LVAD-implanted patients. However, these results were driven almost entirely by higher rates of LVAD implantation in the OMT arm, and not by reduced mortality. Surprisingly, for the 'OMT group', only the use of beta-blockers and ACEIs/ARBs was reported.[3] These combined findings call for re-evaluation of OMT (and its definition) in LVAD candidates.

HF guidelines recommend the use of inotropes in selected patients and only until clinical stabilization.[7,13] However, inotropes are being used in only 1.3–32% of patients hospitalized because of HF.[14] This underutilization is probably explained by physicians' concerns regarding the reported increased mortality observed among inotrope-treated patients.[15,16] It is therefore important to emphasize that data showing increased mortality rates among inotrope-treated patients were extracted mostly from studies conducted in the 1990s, when beta-blockers and implantable cardioverter defibrillators were scarcely used. In contrast, the more recent Studies of Enoximone Therapy in Advanced HF (ESSENTIAL) trial, in which patients were treated with contemporary HF therapy, reported an improvement in HF symptoms in the enoximone arm, with a *neutral effect on mortality*.[17] Considering the beneficial haemodynamic effect of milrinone on CO, systemic and pulmonary vascular resistance, and kidney perfusion,[18] all of our patients were initially treated with

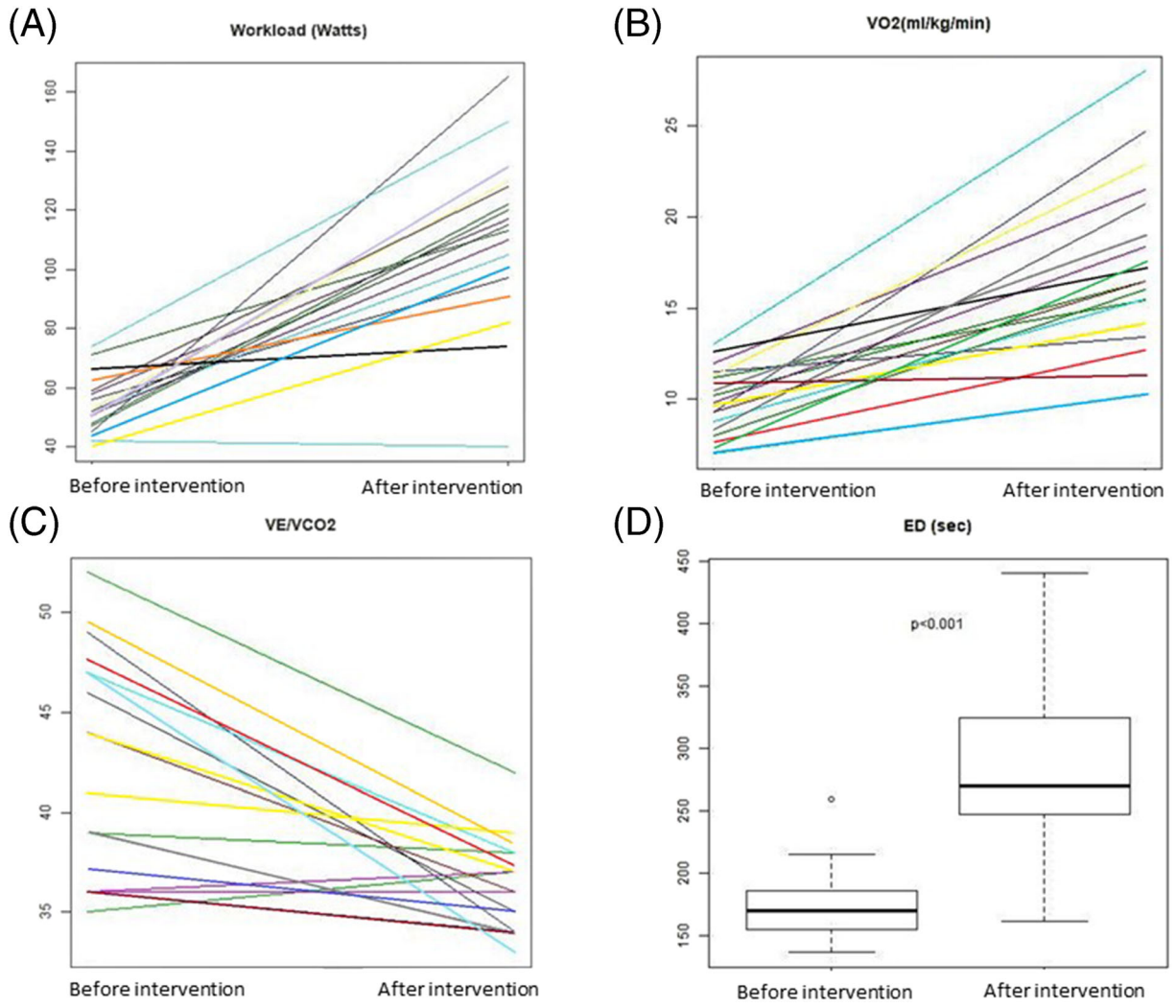
Figure 3 Brain natriuretic peptide (BNP) levels declined after the intervention period.



milrinone. Furthermore, rather than withholding this therapy after initial stabilization, we chose to continue this treatment during the introduction and up-titration of neurohormonal therapy. Evidence shows that the combination of milrinone (which increases cAMP levels in a beta-adrenergic receptor-independent pathway) and beta-blockers allows HF patients to benefit from altered intracellular G-proteins profile and improved haemodynamics while maintaining a low risk for arrhythmias.[19] Of note, despite the intermittent use of milrinone in our study and its known limited (2.5 h) half-life, based on previous publications demonstrating protracted haemodynamic effect following repeated milrinone exposure,[20,21] it is likely that our patients continued to benefit from its haemodynamic effect. Though not currently endorsed by HF guidelines, we recently reported the safety and potential efficacy of intermittent inotropic therapy in advanced HF.[22,23] One may argue that the extended half-life, attenuated increase in oxygen consumption, and reduced arrhythmogenicity shown with levosimendan[24] might prove it to be the inotrope of choice in this setting. Currently, however, most of our experience is with milrinone.

Our active goal was to treat our patients with the highest tolerable doses of guideline-recommended therapy, including appropriate beta-blockers, sacubitril–valsartan, mineralocorticoid receptor antagonists, and, more recently, SGLT2i. Nevertheless, all our patients were initially considered poorly responsive patients with advanced HF, and we believe that less established therapies also contributed to their stabilization. These therapies include the combination of hydralazine and isosorbide dinitrate (H-ISDN), agents that were largely abandoned by HF centres following the introduction of ACEIs. For example, a recent publication showed that only 18.2% of eligible patients were prescribed with H-ISDN at hospital discharge.[25] This underutilization is probably disadvantageous. After all, careful analysis of the second Vasodilator in Heart Failure Trials (V-HeFT II) shows that although a trend towards an overall 2 year mortality reduction was found with the use of enalapril compared with H-ISDN (*P* value was 0.08), a larger elevation in both LVEF and VO_2 max was in fact demonstrated in the H-ISDN-treated patients.[26] Furthermore, the beneficial effect achieved with H-ISDN *in addition* to ACEIs was never tested in the entire HF with reduced ejection fraction (HFrEF) spectrum. Another drug is digoxin, an old and somewhat notorious medication that has recently regained acceptance. Recent studies[27,28] show that the addition of digoxin to guideline-directed therapy was not only safe but also associated with a reduction in HF readmission. We chose to use digoxin in many of our ambulatory patients in order to improve functional capacity and reduce symptoms of fatigue and manoeuvred their stabilization for further neurohormonal drug up-titration. Other less recognized therapies were also utilized in our patient management. Thiamine deficiency is prevalent in HF patients, probably due to low body storage, insufficient nutrition, malabsorption, and increased urinary excretion.[29] Furthermore, small clinical trials have shown that correction of thiamine deficiency may lead to myocardial recovery.[30,31] Because evaluation of thiamine deficiency is frequently inaccurate (either due to strong influence of recent nutritional intake or due to the effect of anaemia), we chose to treat most of our patients with parenteral and oral thiamine supplementation. Vitamin D (shown to increase LVEF in HFrEF patients[32]) and coenzyme Q10 (shown to reduce HF hospitalizations and mortality in HFrEF patients[33]) have not been examined in large-scale clinical trials in HF. However, as both exhibit excellent safety profile, we found it reasonable to utilize these agents as part of our

Figure 4 Exercise capacity, as measured with the use of cardiopulmonary exercise test, improved following the intervention period: (A) workload, (B) maximal oxygen consumption, (C) ventilatory efficiency, and (D) exercise duration (ED).



treatment plan in appropriate patients. Additionally, in light of the improved outcomes shown in cardiac patients treated with drugs from the glucagon-like peptide 1 receptor agonists[34] and the SGLT2i[35,36] families, we actively participated in diabetes management of our patients. Furthermore, given the results of recent HF trials on SGLT2i,[36,37] we rapidly incorporated these drugs as part of our treatment regimen. Importantly, studies have shown that SGLT2i were safe and efficacious even during the early phase of HF admission.[38] Lastly, and as previously demonstrated,[39] our ability to closely monitor selected patients after their initial stabilization at our outpatient HF clinic, where on-site blood tests and intravenous diuretics and inotropes can be utilized by skilled personnel, probably played an important role in our patients' outcome.

The concept of myocardial recovery is gaining more and more attention in the HF community. Recently, Birks *et al*. reported that in a group of 36 end-stage non-ischaemic HF patients who underwent an LVAD implantation and received aggressive neurohormonal therapy, the device could be eventually explanted for 19 (52%) patients.[40] Furthermore, a relatively short disease duration was found to be associated with improved chances for recovery.[41] Notably, these findings are consistent with those presented in our study (*Table 1*). Examining the intracellular level, Seidel *et al*. demonstrated that myocardial biopsies taken from end-stage HF patients with a similar degree of myocardial dysfunction show dissimilarities in the T-tubule structure, which predict post-LVAD myocardial recovery.[42] Additionally, Nagaraju *et al*. showed that myofibroblasts, responsible for myocardial fibrosis in ad-

Figure 5 Following intervention, echocardiographic parameters improved: (A) Left ventricular dimensions decreased, (B) cardiac output (CO) increased, and (C) diastolic function improved. LVEDD, left ventricular end-diastolic diameter.

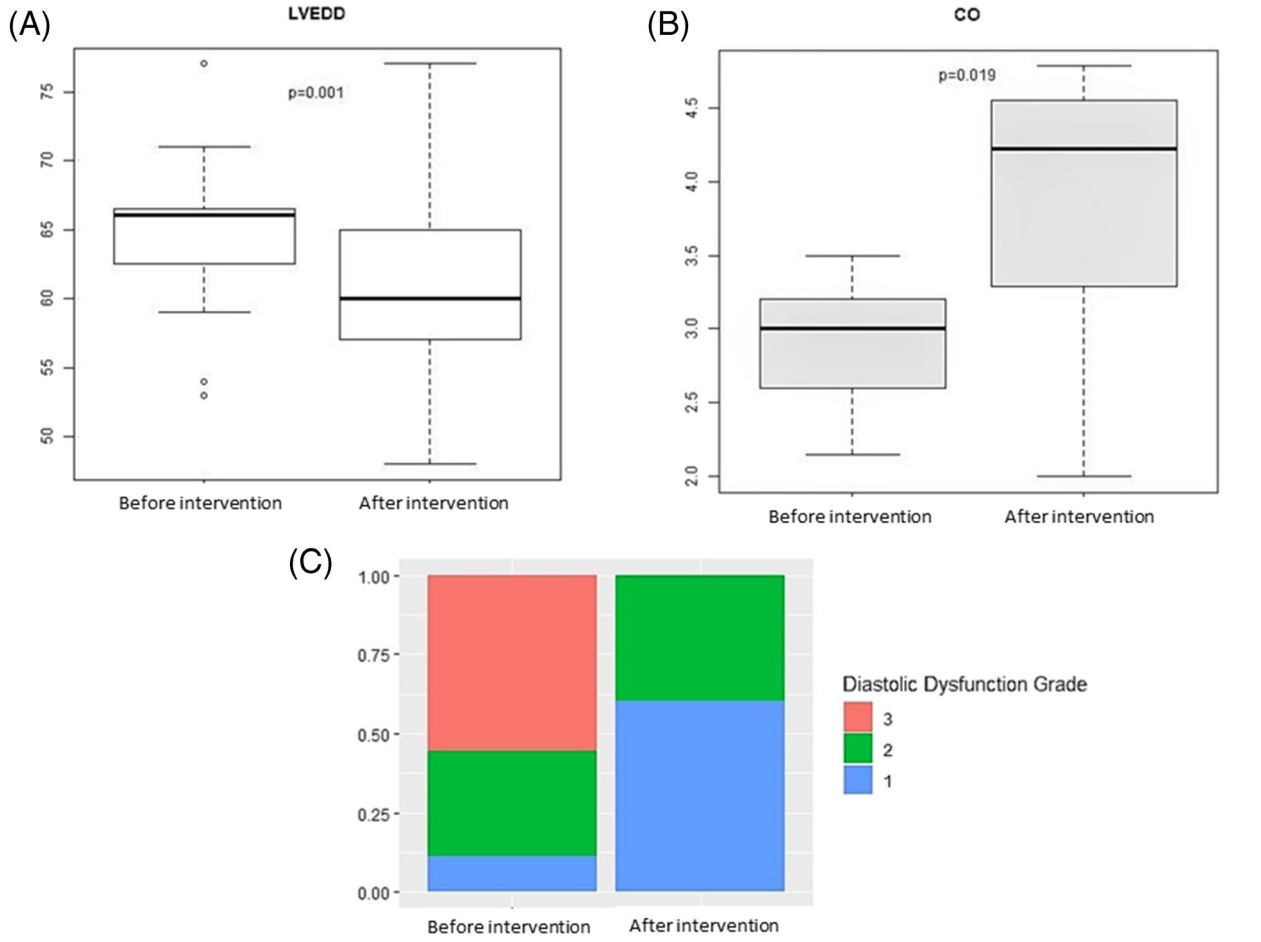


Table 3 Hospitalizations and day-care visits in the 12 months before and after the intervention

	Admission days, before	Admission days, after	Day-care visits, before	Day-care visits, after
LVAD	42, 27, 41	25, 55, 117	26, 3, 4	6, 12, 7
No LVAD	9 (0–41)	7 (0–52)	5 (0–22)	8 (0–29)

LVAD, left ventricular assist device.

vanced HF, retain the capacity to regress to a non-active state and might be involved in the reverse remodelling process.[43] These findings greatly contribute to the notion that myocardial recovery can be reached even in advanced stages of HF and might explain our findings.

Our approach could be criticized as exposing advanced HF patients to the risk of swift clinical deterioration and possible death due to postponement of LVAD implantation. Nevertheless, as mentioned previously, the results of the ROADMAP study[3] show that although survival on initial therapy was reached in a higher proportion in the LVAD group, it was driven mainly by more LVAD implantations in the OMT group and not by survival benefit per se, implying to the safety of LVAD deferral in these patients.

This study has several limitations. First, its small size and the lack of comparator group prevent us from reaching more definitive conclusions. In this regard, it is important to note that the seminal trials on LVAD-induced myocardial recovery[44,45]—which showed results similar to those shown here for OMT—were conducted in groups of 20 and 21 patients, respectively, and did not include a control group. Second, the patients included in the study were relatively stable and did not have extreme (i.e. Class 1 or 2) INTERMACS profiles. Nevertheless, our patients' profile is similar to that of

Table 4 Medical therapy of left ventricular assist device candidates in large contemporary series

	Study, publication year		
Therapy, % used	MOMENTUM 3, 2017	ENDURANCE, 2017	ROADMAP, 2015
BBs	58	55.5	91.5
ACEIs/ARBs	35	30	72.5
MRAs	Not reported	Not reported	Not reported
Sacubitril/valsartan	Not reported	Not reported	Not reported
Dapagliflozin/empagliflozin	Not reported	Not reported	Not reported
Hydralazine and nitrates	Not reported	Not reported	Not reported
Diuretics	92	81	100

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BBs, beta-blockers; ENDURANCE, The HeartWare Ventricular Assist System as Destination Therapy of Advanced Heart Failure study; MOMENTUM 3, Multicenter Study of Magnetically Levitated Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3; MRAs, mineralocorticoid receptor blockers; ROADMAP, Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management study.

~67% of LVAD candidates in recent large studies.[4,5] Third, a significant proportion of these patients continue to receive intermittent inotropes and are closely followed at our outpatient clinic. Still, their hospitalization rate remains low and they maintain reasonable ambulatory activity.

In conclusion, our findings suggest that in the proper setting, and under close follow-up, a significant number of LVAD implantations can be safely avoided or at least postponed, without exposing patients to excessive risk. Also, although the small scale of our cohort prevents clear conclusions, we believe that these results call for a clinical trial comparing LVAD implantation vs. contemporary OMT.

Conflict of interest

None declared.

Funding

None.

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