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Intensive titration for elderly patients with heart failure

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ABSTRACT

Background Guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF) relies on quadruple therapy, including beta-blockers (BB), angiotensin receptor–neprilysin inhibitors (ARNi), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i). Elderly patients with HF represent a high-risk population and often face therapeutic inertia but also more adverse events. We aimed to assess the efficacy and safety of an intensive titration program (ITP) for elderly HFrEF patients.

Methods We conducted a prospective, single-center, observational study including HFrEF patients aged ≥ 75 years managed with an ITP between January 2024 and February 2025. The primary outcome was the prescription rate of quadruple GDMT at 3 months, irrespective of dose. Secondary outcomes included prescription of quadruple therapy at ≥ 50% of GDMT target doses and identification of predictors of limited implementation. Safety outcomes included adverse events occurring during titration and within 3 months after completion.

Results Sixty-four patients were included (Median age 80 years, 70% male, 28% diabetes, median eGFR 50 mL/min). The mean titration period was 100 days (14 weeks). At 3 months, 33% of patients were prescribed quadruple therapy, with 5% achieving ≥ 50% of the recommended target dose in each drug class. Target dose achievement improved across all drug classes between baseline and 3 months: ARNi (1% *vs.* 31%), MRA (1% *vs.* 14%), and BB (3% *vs.* 5%) (all P <0.05). These improvements were associated with short-term clinical and biological benefits (NT-proBNP reduction, improved left ventricular ejection fraction). Reported adverse events included symptomatic hypotension (8% with treatment discontinuation) and acute kidney injury (8 % requiring hospitalization). Older age and chronic kidney disease were associated with limited initiation of quadruple therapy.

Conclusion An intensive titration program for HFrEF therapy appears feasible and relatively safe in elderly patients.

Chronic heart failure (HF) remains a major public health issue, affecting approximately 2.6% of the adult population in France.[1] In patients over 80 years of age, a first hospitalization for HF is followed by a particularly high rate of rehospitalization and/or death at two years (85%).[2] Since 2021, European guidelines recommend the early initiation of a four-drug regimen including renin–angiotensin system inhibitors (ACE/ARB/ARNi), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i) for all heart failure with reduced ejection fraction (HFrEF) patients.[3] However, the practical modalities of dose titration remain unclear, and available data are contradictory between randomized trials and real-world settings.[4] While the STRONG-HF trial demonstrated the feasibility and safety of a rapid titration program after hospitalization for acute decompensated HF,[5] real-world studies have highlighted significant gaps in the optimization of HFrEF therapy,[6] showing a high rate of quadruple therapy prescription but with doses frequently below target doses. As a result, treatment optimization often remains suboptimal, frequently limited by comorbidities such as renal dysfunction,[7] hypotension,[8] or bradycardia.[9,10]

This challenge is particularly relevant in elderly patients, where the prevalence of HFrEF is steadily increasing. Several studies have highlighted that octogen-

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arians are undertreated compared with younger patients, despite their higher risk of adverse outcomes.[11] In this population, frailty plays a crucial role, reflecting physical and cognitive vulnerability that amplifies the burden of heart failure.[12,13] The high prevalence of comorbidities, polypharmacy, and increased susceptibility to adverse effects further complicate rapid titration strategies.[14-16]

To address these issues, we developed an intensive titration program (ITP), which has previously demonstrated its efficacy in overcoming therapeutic inertia without increasing adverse events.[17] Whether this strategy is safe and effective in older patients, however, remains unclear. We therefore conducted a study to evaluate the feasibility, safety, and efficacy at 3 months of an ITP in HFrEF patients aged 75 years and older.

METHODS

Study Design and Population

This was a prospective, single-center, observational, and descriptive study conducted at Toulouse University Hospital between January 2024 and February 2025. HFrEF patients (LVEF < 40%) aged 75 years or older were included. Patients with end-stage renal disease on dialysis, those followed by a cardiologist outside our hospital, patients under legal protection (guardianship or trusteeship), and patients without health insurance coverage were excluded from the present analysis.

According to French ethics and regulatory law (Public Health Code), all patients received information about anonymized data collection. Written informed consent for participation was not required for this study in accordance with the national legislation. The study was registered by the Toulouse University Hospital (registration number: RnIPH 2025-122) and covered by the MR-004 methodology.

Data Collection

Baseline data were collected prospectively at the time of inclusion, including demographics (sex, age, occupation, place of residence), medical history, cardiovascular risk factors, underlying etiology of cardiomyopathy, disease onset mode, clinical data (blood pressure, heart rate, NYHA functional class I–IV), laboratory values (serum creatinine, estimated glomerular filtration rate [eGFR], potassium, NT-proBNP, albumin), and echocardiographic parameters (LVEF, left ventricular end-diastolic diameter (LVEDD), indexed end-diastolic volume (LVEDVi), TAPSE, tricuspid S wave. To define frailty, the Triage Risk Screening Tool (TRST), a reliable predictor of emergency readmission for elderly,[18] and the Fried frailty score were assessed by a specialized heart failure nurse. A 6-min walk test and maximal handgrip strength were also performed.

Modalities of cardiology follow-up and enrollment in remote monitoring or the PRADO program (French post-discharge home care support program) were collected at discharge,[19] Regarding HF therapies, drug prescriptions and dosages were recorded at three time points: baseline (hospital discharge or outpatient clinic), after completion of the intensive titration protocol, and three months after the end of the protocol (3-month follow-up). For MRA, BB and ACEi/ARB/ARNi classes, dosages are reported as % of the GDMT target dose per the 2021 ESC guidelines (Appendix S2).

Intensive Titration Program (ITP)

Initiation of guideline-recommended therapeutic classes for HFrEF was left to the discretion of the treating physician, according to hemodynamic and biological tolerance. The ITP was initiated once patients were referred to the dedicated team for intensive optimization of HFrEF therapy. The first titration visit was generally conducted in the outpatient day-care unit, during which a comprehensive geriatric assessment was performed as previously described. Subsequent titration visits were carried out either on-site or remotely via the TeleO® telemedicine platform, jointly by a cardiologist and a specialized nurse. Clinical, laboratory, and hemodynamic parameters were obtained through remote monitoring or self-measurements prior to each therapeutic adjustment. Decisions regarding drug initiation or dose escalation were made at the discretion of the treating physician, based on clinical status and laboratory findings. Prescriptions were adapted accordingly and transmitted to the patient or the appropriate healthcare professional. Dedicated visits focused exclusively on heart failure medication titration were scheduled at intervals of 2 to 4 weeks. Additional in-person or teleconsultations were arranged if the patient had not yet reached the maximum tolerated dose or if an adverse event required treatment modification. Titration follow-up continued until the maximum tolerated doses were achieved, after which patients returned to standard care, including a

follow-up visit at 3 months. At 3 months, clinical, biological, and echocardiographic follow-up data were collected by the referring cardiologist.

Outcomes

The primary endpoint was defined as prescription rate of quadruple therapy (ARNi/ACEi/ARB, BB, MRA, SGLT2i) of GDMT 3 months after ITP whatever the dosage obtained for each drug class.

Secondary outcomes included the prescription rate of quadruple therapy (ARNi/ACEi/ARB, BB, MRA, SGLT2i) at ≥ 50% of GDMT at 3 months, according to the algorithm proposed by Girerd, *et al.*,[18] and to the predictors of non-implementation of each drug class and of failure to achieve target dosing.

Safety outcomes included adverse events during titration and within 3 months after completion. The primary safety outcome was severe adverse events (acute kidney injury, hyperkalemia, or syncope due to bradycardia requiring hospitalization). Secondary safety outcomes were minor adverse events, including acute kidney injury (creatinine increase > 30%), hyperkalemia (> 5.5 mmol/L or requiring potassium binders), symptomatic hypotension, bradycardia requiring treatment adjustment, cough, urinary/genital infection, and gastrointestinal symptoms.

Statistical Analysis

Quantitative variables were expressed as medians with interquartile ranges (IQR), and qualitative variables as counts and percentages. Comparisons were performed using the Mann–Whitney test for quantitative variables, and χ^2 or Fisher's exact tests for qualitative variables. For each drug class of interest, a multivariable logistic regression model was constructed to identify predictors of suboptimal prescription, adjusting for age, body mass index, TRST score, history of ischemic heart disease, hypertension, or diabetes, LVEF, NT-proBNP, and serum creatinine. Two separate analyses were conducted: one assessing achievement of an optimal therapeutic dose (≥ 50% of GDMT), the other assessing initiation of therapy irrespective of dose. Covariates were selected based on clinical relevance and likelihood of association with outcomes, following the PROGRESS (Prognosis Research Strategy) recommendations.[20] Results are presented as odds ratios (OR) with 95% confidence intervals.

To evaluate global titration, a titration score was constructed based on prescribed doses: BB (+1: any dose; +2: ≥ 50% target dose), ACEi/ARB/ARNi (+1: any dose; +2: ≥ 50% target dose), MRAs (+1: any dose; +2: ≥ 50% target dose), and SGLT2i (+1: any dose). A score <4 defined suboptimal titration. Statistical analyses were performed using Prism (GraphPad Software, San Diego, CA, USA) and R Studio (version 4.3.2, 2023-10-31).

RESULTS

Study Population

A total of 64 patients were prospectively enrolled between January 2024 and February 2025 (Table 1). The median age was 80 years (IQR 77–83), and 70% were male. Etiologies (not exclusive) of cardiomyopathies were ischemic for 67% (n = 43), arrhythmic for 32% (n = 21), and dilated for 16% (n = 10).

Most patients (86%, n = 55) were included at hospital discharge, with a median length of stay of 6.5 days (IQR: 3–11). The main cause of admission was acute decompensated HF (47%, n = 30), followed by elective hospitalization for HF evaluation (37%, n = 24). At discharge, 20% (n = 13) of patients were enrolled in the PRADO program and 20% (n = 13) in remote monitoring.

At baseline, median NT-pro-BNP was 2736 pg/mL (IQR 1426–5153), median creatinine 116 µmol/L (IQR 89–150), mean serum potassium 4.2 ± 0.4 mmol/L, and median albumin 36 g/L (IQR 32–39). Echocardiography showed a median LVEF of 35% (IQR 25–40).

Regarding geriatric profile, 70% (n = 45) had a TRST score ≥ 2. According to the Fried score, 5% were robust, 25% pre-frail, and 25% frail. with reduced handgrip strength and a mean 6-minute walk distance of 273 m (45% predicted value).

Patients in whom quadruple therapy was not prescribed were characterized by older age (81 *vs.* 78 years; P = 0.015), more severe symptoms (NYHA class; P = 0.016), and higher plasma creatinine levels (131 *vs.* 97 µmol/L; P = 0.008).

Feasibility and Efficacy of Intensive Titration Therapy

The mean duration of the titration protocol was 100 ± 79 days (14 weeks), requiring on average three visits. Only four patients completed the program exclusively via teleconsultation. At the end of the intensive titration program, 38% of patients (n = 24) were on quadruple therapy at any dose and 34% (n = 22) on triple therapy

Table 1 Baseline characteristics of patients (*n* = 64).

Characteristic	Total population (*n* = 64)	Subgroup with successful initiation of HFrEF quadruple therapy (*n* = 21)	Subgroup with failed initiation of HFrEF quadruple therapy (*n* = 43)	*P*-value
Men	44 (70%)	13 (62%)	31 (72%)	0.566
Women	20 (31%)	8 (38%)	12 (28%)	-
Median age	80 (77-83)	78 (75-81)	81 (78-85)	0.015
Underlying cardiac disease				
Ischemic cardiomyopathy	43 (67%)	15 (71%)	28 (65%)	0.778
Dilated cardiomyopathy	10 (16%)	5 (24%)	5 (12%)	0.275
Amyloid cardiomyopathy	1 (2%)	1 (4%)	0	> 0.999
Hypertensive cardiomyopathy	4 (6%)	1 (4%)	3 (7%)	> 0.999
Arrhythmic cardiomyopathy	21 (33%)	5 (24%)	16 (37%)	0.397
Valvular cardiomyopathy	11 (17%)	2 (9%)	9 (21%)	0.314
Disease duration				
First episode	25 (39%)	11 (52%)	14 (33%)	0.174
Known cardiac follow-up	43 (67%)	11 (52%)	32 (74%)	0.094
Cardiac history				
Coronary angioplasty	37 (58%)	13 (62%)	24 (56%)	0.788
CABG	8 (13%)	3 (14%)	5 (12%)	0.384
Atrial fibrillation	28 (44%)*	7 (33%)	21 (49%)	0.290
TAVI	1 (2%)	0	1 (2%)	-
Cardiovascular risk factors				
Hypertension	47 (73%)	17 (81%)	30 (70%)	0.385
Type 2 diabetes	18 (28%)	5 (24%)	13 (30%)	0.769
Dyslipidemia	37 (58%)	13 (62%)	24 (56%)	0.788
Active smoking	4 (6%)	1 (5%)	3 (7%)	> 0.999
Former smoker	17 (26%)	7 (33%)	10 (23%)	0.547
Status at inclusion				
Outpatient	9 (14%)	1 (5%)	8 (19%)	0.251
Hospitalized	55 (86%)	20 (95%)	35 (81%)	0.251
Length of hospital stay, median days (IQR)	6.5 (3-11)	6 (4-9)	7 (2-12)	0.912
Reason for hospitalization				
Scheduled heart failure assessment**	24 (37%)**	8 (43%)	16 (37%)	> 0.999
Acute coronary syndrome	10 (16%)	4 (19%)	6 (14%)	0.717
Acute heart failure	30 (47%)	9 (43%)	21 (49%)	0.791
Single- or dual-chamber pacemaker	9 (14%)	4 (19%)	5 (12%)	0.459
Remote monitoring	13 (20%)	7 (33%)	6 (14%)	0.099
National transitional home-care program	13 (20%)	2 (9%)	11 (20%)	0.191
Clinical data at inclusion				
Systolic BP, mmHg,	116 (103–123)	120 (109–128)	112 (101–124)	0.122
Diastolic BP, mmHg	65 (57–70)	65 (58–78)	65 (56–70)	0.338
Heart rate, beats/min	71 ± 14	68 (60–82)	70 (60–78)	0.693
NYHA				0.016

Continued

Characteristic	Total population (n = 64)	Subgroup with successful initiation of HFrEF quadruple therapy (n = 21)	Subgroup with failed initiation of HFrEF quadruple therapy (n = 43)	P-value
I	19 (30%)	9 (43%)	10 (23%)	
II	34 (53%)	12 (57%)	22 (51%)	
III	11 (17%)	0	11 (25%)	
IV	0	0	0	
Biological data at inclusion				
NT-proBNP, pg/mL	2736 (1426–5153)	2192 (1015–4795)	2737 (1522–6320)	0.428
Creatinine, µmol/L	116 (89–150)	97 (79–117)	131 (97–168)	0.002
GFR, mL/min	50 ± 20	57 (47–75)	40 (30–56)	0.008
Potassium, mmol/L	4.2 ± 0.4	4.1 ± 0.4	4.3 ± 0.4	0.678
Albumin, g/L	36 (32–39)	37 (35–40)	33 (30–39)	0.105
Echocardiographic data at inclusion				
LVEF, %	35 (25–40)	31 (23–35)	38 (30–40)	0.017
iLVEDV, mL/m^2	78 (59–95)	89 (64–99)	73 (57–87)	0.087
TAPSE, mm	17 ± 5	17 ± 5	17 ± 5	0.713
S wave, cm/s	9 (9–12)	9 (8–12)	9 (8–12)	0.908
Geriatric assessment at inclusion				
TRST score	2 (1–3)	2 (1–2)	2 (1–3)	0.322
Score 0	6 (9%)	2 (9%)	4 (9%)	
Score 1	13 (20%)	6 (29%)	7 (16%)	
Score ≥ 2	45 (70%)	13 (62%)	32 (75%)	
Fried frailty score	2.5 (1–4)***	2.5 (1–3.5)****	2.0 (2–4) *****	0.726
Score 0	3 (5%)	1 (5%)	2 (5%)	
Score 1–2	16 (25%)	5 (24%)	11 (26%)	
Score > 3	16 (25%)	6 (29%)	10 (23%)	
Handgrip strength (men), mean, kg	34.5 ± 4	37 ± 7	33 ± 5	0.684
Handgrip strength (women), mean, kg	14.7 ± 5	17 ± 5	16 ± 4	0.611
6-min walk test, mean distance, m (% predicted value ******)	273 (45%)	230 (37%)	288 (46%)	0.354

Data are presented as n (%), mean ± SD or median (IQR). Comparison between the subpopulation with successful prescription of quadruple therapy vs subpopulation with failure of prescription of quadruple therapy at 3M by Student's t-test if values are normal, by Fisher's test if values are binary, by Mann–Whitney test if non-normal or ordinal. *Of which 11 paroxysmal, 11 persistent and 6 permanent; ** of which 9 in day hospital (HDJ); *** calculated in 35 patients; **** calculated in 12 patients; ***** calculated in 23 patients; ****** Expected distance for a six-minute walk test: (T6) in meters = 218 + [5,14 X height in cm] – [5,32 X age] – [1,8 X weight in kg] + [51,31 X sex] (0 for female and 1 for male). ACS: Acute coronary syndrome; AHF: Acute heart failure; CABG: Coronary artery bypass graft; HFA: Heart failure assessment; HTN: Hypertension; LVEDD: Left ventricular end-diastolic diameter; LVEDV: Left ventricular end-diastolic volume; LVEF: Left ventricular ejection fraction; PM: Pacemaker; T2DM: Type 2 diabetes mellitus; TAVI: Transcatheter Aortic Valve Implantation.

(Figure 1A). Importantly, at 3 months, one-third of patients (n = 21) were prescribed quadruple therapy (Figure 1A).

During follow-up, GDMT was progressively optimized (Figure 2): 31% of patients reached the maximum sacubitril/valsartan dose (97/103 mg) at 3 months, with increased use of MRAs and BB at ≥ 50% of the target dose. Among patients who achieved the target heart rate (< 70 beats/min), control was obtained with BB therapy at only 28% of the GDMT target dose on average. In parallel, high-dose loop diuretic prescriptions (≥ 120 mg furosemide) decreased from 28% at baseline to 23% at 3 months.

Regarding treatment intensity, 13% of patients (n = 8) achieved quadruple therapy at ≥ 50% of the target GDMT dose by the end of the program, but only 5% (n =

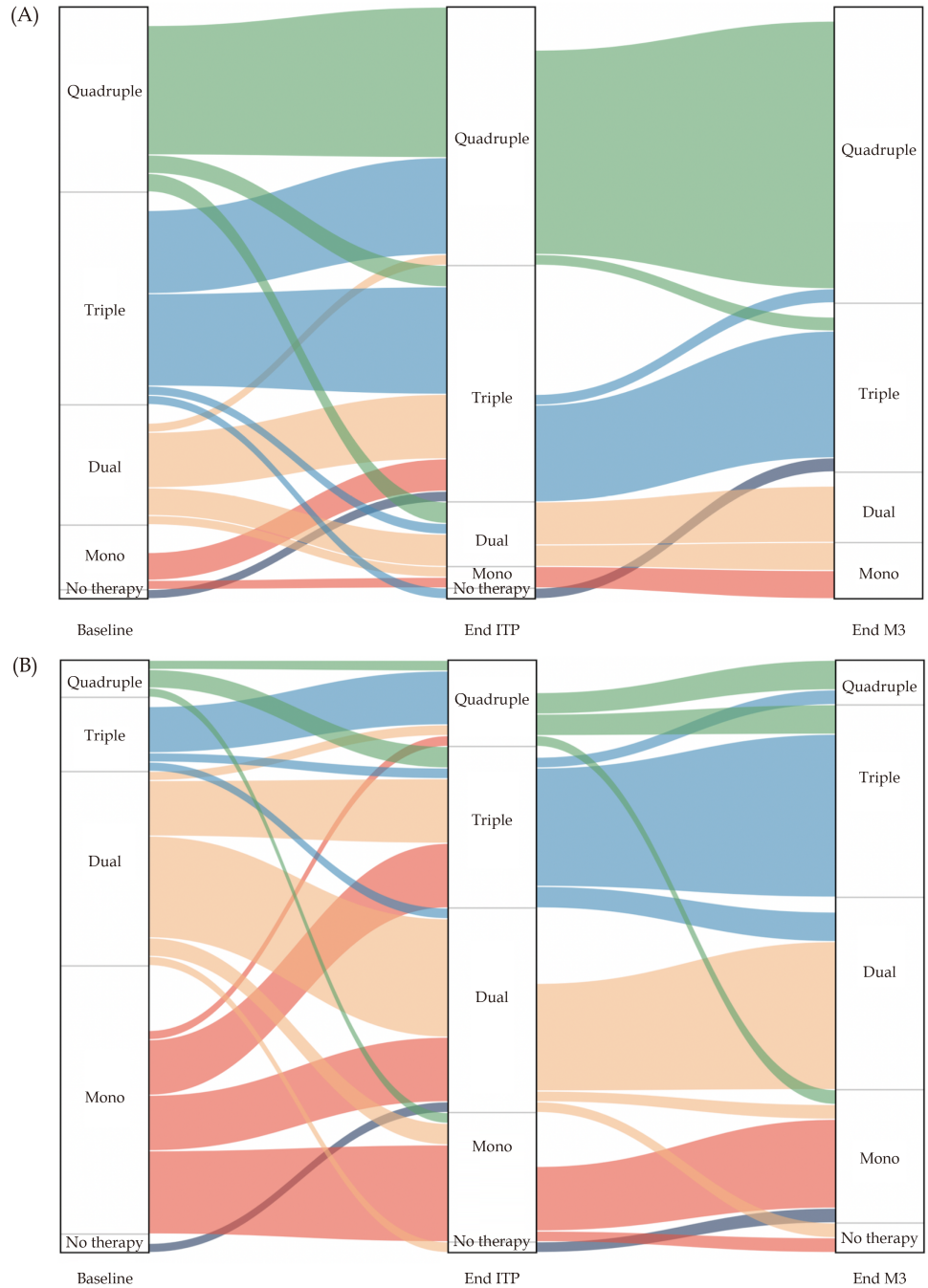


Figure 1 Dynamic distribution of patient numbers by combinations of prescribed therapies (alluvial diagram). Inclusion = at baseline (n = 64); end of ITP = at completion of the intensive titration program (n = 55); M3 = 3 months after completion of the ITP program (n = 42). **A.** Distribution of patient counts by the number of prescribed therapies, all doses included (therapy initiation), at the end of the intensive titration program and at 3 months. Inclusion: no therapy n = 1 (2%), monotherapy n = 7 (11%), dual therapy n = 13 (20%), triple therapy n = 23 (36%), quadruple therapy n = 20 (31%). End ITP: no therapy n = 1 (2%), monotherapy n = 2 (3%), dual therapy n = 6 (9%), triple therapy n = 22 (34%), quadruple therapy n = 24 (38%). End M3: monotherapy n = 4 (6%), dual therapy n = 5 (19%), triple therapy n = 12 (19%), quadruple therapy n = 21 (33%). **B.** Distribution of patient counts by the number of prescribed therapies with dosing >50% of GDMT-dose, at the end of the intensive titration program and at 3 months. Inclusion: no therapy n = 2 (3%), monotherapy n = 29 (45%), dual therapy n = 21 (33%), triple therapy n = 8 (13%), quadruple therapy n = 4 (6%). End of ITP: no therapy n = 1 (2%), monotherapy n = 12 (19%), dual therapy n = 19 (30%), triple therapy n = 15 (23%), quadruple therapy n = 8 (13%). M3: no therapy n = 2 (3%), monotherapy n = 11 (17%), dual therapy n = 13 (20%), triple therapy n = 13 (20%), quadruple therapy n = 3 (5%). GDMT: guided-directed medical therapy. ITP: Intensive Titration Program.



Figure 2 Trends in HFrEF treatment dosages. Baseline (n = 64); End of ITP (n = 55); 3-month follow-up (n = 42) For the MRA, beta-blocker, and ACEi/ARB classes, dosages are reported as % of the guideline- recommended target dose per the 2021 ESC guidelines (Appendix S2). ITP: intensive titration program. M3: 3-month follow-up. ACEi: Angiotensin-Converting Enzyme inhibitor; ARB: Angiotensin II Receptor Blocker; ARNi: Angiotensin Receptor–Neprilysin Inhibitor; BB: Beta-Blocker; MRA: Mineralocorticoid Receptor Antagonist; SLGT2 inhibitor: Sodium–Glucose Cotransporter 2 inhibitor.

3) maintained this at 3 months (Figure 1B). At that time point, 41% of patients (n = 26) were on dual or triple therapy at ≥ 50% of the target dose.

At 3 months, positive cardiac remodeling was observed (Figure 3), with significant improvement in LVEF (P < 0.0001), blood pressure profile (P < 0.001), and NT-pro-BNP levels (P < 0.001). A significant reduction in heart rate was observed, with a mean value of 62 beats/min at 3 months. NYHA class did not differ between baseline and follow-up.

Security/Adverse Events

Table 2 describes all adverse events observed during follow-up. Symptomatic hypotension occurred in 16 patients (28%) of which 5 (9%) led to drug withdrawal. Acute kidney injury occurred in 19 (33%) whose 5 (9%) required hospitalization. Hyperkalemia led to treatment withdrawal in 5% (n = 3), but no hospitalizations. Bradycardia required treatment adjustment in 14% (n = 8), with one requiring hospitalization. Serum creatinine and potassium remained stable, with no significant changes at 3 months follow-up (Figure 3).

Predictors of Limited Therapy Implementation

Age was also a limiting factor for initiation of ACEi/ARB/ARNi and of quadruple therapy overall (OR = 1.18 and OR = 1.13, respectively) (Table 3 and appendix S3). Higher baseline creatinine was associated with increased risk of not receiving MRAs (OR = 2.2), ACEi/ARB/ARNi (OR 1.6), or quadruple therapy (OR = 1.4) at 3 months.

The increase in age and chronic kidney disease (CKD) at baseline were associated with limited quadruple therapy titration (OR = 1.61 and OR = 2.79, respectively) (Table 3). CKD specifically limited MRA titration (OR = 2.20) but was associated with easier BB prescription (OR = 0.60) (Appendix S4). A higher TRST score was also associated with limited MRA titration: each additional TRST point decreased the likelihood of up-titration by a factor of four (OR = 3.67) (appendix S4). No predictors of

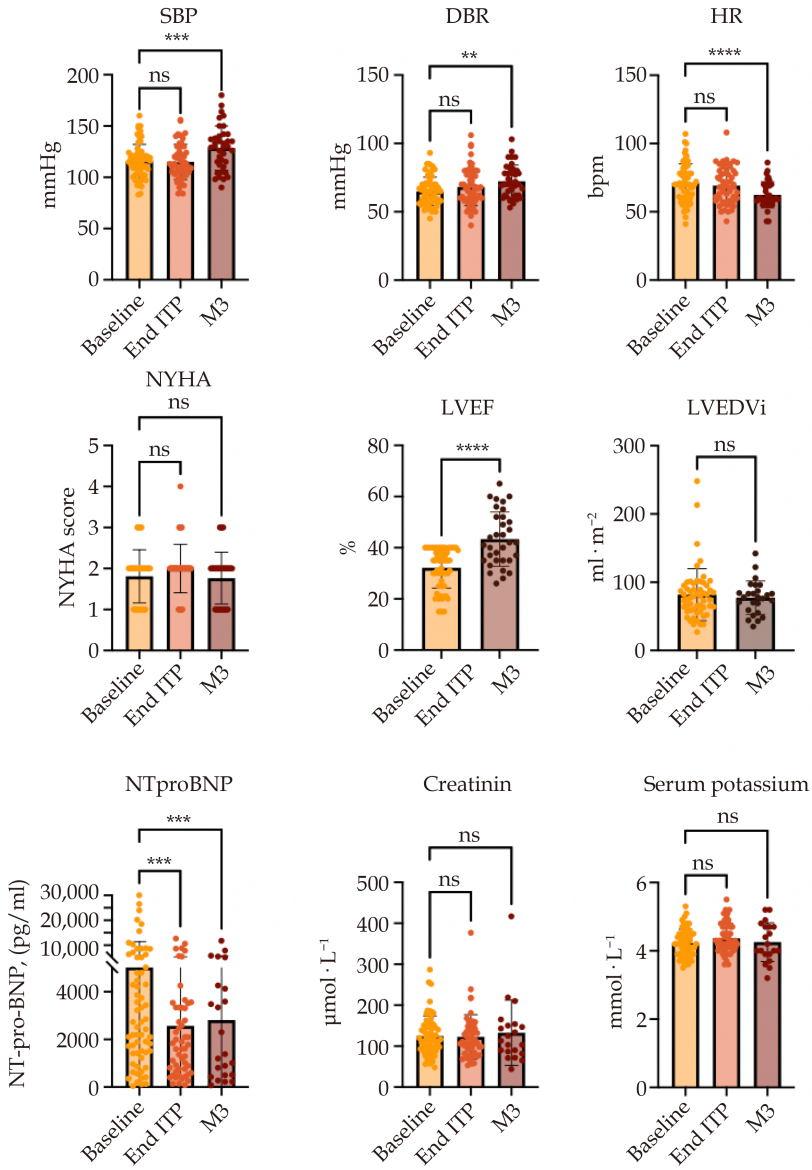


Figure 3 Evolution over time of clinical, echocardiographic, and biological data. End ITP: at the completion of the intensive titration program for heart failure. End M3: data collected 3 months after the completion of the intensive titration program (ITP) program for heart failure. DBP: diastolic blood pressure; EF: Ejection fraction; HR: heart rate; SBP: systolic blood pressure; VTDVGi: Left ventricular end-diastolic volume indexed.

limited titration were identified for BB or ACEi/ARB/ARNi (appendix S4). A history of hypertension was associated with facilitated prescription of quadruple therapy, particularly MRAs and ACEi/ARB/ARNi (appendix S4).

DISCUSSION

To our knowledge, this is the first study specifically assessing the feasibility and safety of intensive GDMT titration in patients aged ≥ 75 years with HFrEF. Our results show that a rapid titration protocol is feasible in this population, with one-third of patients receiving quadruple therapy at 3 months and 5% reaching at least 50% of the target dose for each drug class; tolerability is acceptable, with fewer than 10% requiring drug withdrawal or hospitalization.

We showed that rapid optimization of quadruple therapy is feasible in frail or pre-frail patients with 33% of patients on quadruple therapy at 3-month which is con-

Table 2 Adverse events observed during the observational study.

Adverse events	*N* (%)
Symptomatic hypotension	16 (25)
Dose reduction	11 (17)
Treatment discontinuation	5 (8)
Acute kidney injury (increase in serum creatinine >30%)	19 (30)
Hospitalization	5 (8)
Treatment discontinuation	9 (14)
Hyperkalemia (serum potassium >5.5 mmol/L)	3 (5)
Hospitalization	0 (0)
Treatment discontinuation	3 (5)
Bradycardia	9 (14)
Syncope or hospitalization	1 (2)
Beta-blocker dose reduction	5 (8)
Beta-blocker discontinuation	3 (5)
Urinary tract infection, pelvic infection, or digestive disorders	3 (5)

Table 3 Limiting factor for initiation or up-titration of HFrEF quadruple therapy.

	Limited initiation of quadruple therapy		Limited titration of quadruple therapy	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.13 (1.02–1.25)	0.02	1.61 (1.13–2.95)	0.03
BMI	0.97 (0.87–1.08)	0.59	1.03 (0.78–1.35)	0.84
TRST score	1.16 (0.70–1.93)	0.56	0.36 (0.03–1.88)	0.27
Ischemic cardiopathy	0.52 (0.17–1.61)	0.26	1.83 (0.05–14.2)	0.74
Hypertension	0.45 (0.15–1.35)	0.15	0.20 (0.10–0.75)	0.02
Type 2 diabetes	2.49 (0.74–8.33)	0.14	0.29 (0.09–3.97)	0.63
LVEF, per 10% increase	1.60 (0.84–3.04)	0.15	1.39 (0.18–18.7)	0.76
NT-proBNP, per 500 pg/mL increase	0.99 (0.95–1.03)	0.61	0.97 (0.80–1.09)	0.61
Creatinine, per 20 μmol/L increase	1.36 (1.08–1.71)	< 0.01	2.79 (1.48–9.04)	0.02

BMI: body mass index; FEVG: left ventricular ejection fraction; OR: odds ratio; TRST: Triage Risk Screening Tool.

sistent with the 47% of patients on quadruple therapy initiated within 6 weeks in the TITRATE-HF cohort (median age 71 years).[6] But, as previously observed dose optimization remained limited with only 13% achieving quadruple therapy at ≥ 50% dose at the end of our ITP and only 5% maintaining it at 3-month follow-up (14% reached at least half of the target dose across all four classes, and just 1.2% achieved full target doses at 6 weeks in the TITRATE-HF cohort).

Notably, 31% of our patients achieved target doses of ARNi, a rate higher than that reported in CHAMP-HF,[4] ASIAN-HF,[21] and TITRATE-HF[6] (14%, 13%, and 28%, respectively). By contrast, fewer patients in our cohort achieved target doses of β-blockers (5 *vs.* 28% in CHAMP-HF and 13% in TITRATE-HF); or MRAs (14% *vs.* 76% in CHAMP-HF and 14% in TITRATE-HF). This discrepancy likely reflects our strategy of prioritizing maximal ARNi dosing in accordance with the recent 2024 ACC expert consensus arguing that ARNi initiation is often better tolerated when patients remain wet.[13]

Moreover, β-blocker dose optimization per the pro-

tocol of Girerd, *et al*.[18] remained suboptimal in our cohort, with 71% of patients receiving < 50% of the guideline-recommended target dose at the end of the ITP. This limitation is partly attributable to heart-rate constraints in our study population as frequently observed in clinical practice. Importantly, several studies have shown that the efficacy of this class correlates more with achieving a specific target heart rate than with a target dose.[22]

Among elderly patients, RAAS overactivation suggests that MRAs offer the greatest benefit; nevertheless, our data indicate that baseline renal dysfunction substantially restricts their use (OR 1.61 for limited quadruple therapy use and 2.20 for MRA use in our cohort). The mean titration duration in our study was 100 days (14 weeks), substantially longer than guideline recommendations and longer than the 10 weeks observed in younger patients managed with the same ITP at our center.[17] This reflects the greater comorbidity and severity of elderly patients in our cohort, who had a lower baseline eGFR (50 *vs.* 71 mL/min per 1.73 m^2) and higher NT-proBNP (2736 *vs.* 1322 pg/mL) compared with younger patients.

In our cohort, adverse events were common, with renal and hemodynamic intolerance predominating. Severe events, mainly acute kidney injury and bradycardia without severe hyperkalemia remained below 10%. In the STRONG-HF trial,[23] adverse events were frequent but less severe even in the sub-analysis of patients over 65 years,[24] likely reflecting our older and frailer patients (LVEF 35% and median age 80 years as compared with LVEF 39% and mean age 74 years for the STRONG-HF seniors). Although therapeutic intensification is more challenging in elderly patients, it was generally well tolerated.

In contrast to STRONG-HF, advanced age in our cohort appeared to limit the implementation of optimal quadruple therapy, probably due to greater therapeutic inertia in real life practice. Frailty assessment is essential to better discriminate patient phenotypes. The TRST score has recently been proposed for use in cardiology [25] and appears easy to administer by non-specialists, even in outpatient settings. However, in HFrEF patients, the high number of medications may artificially inflate the score, potentially overestimating frailty and discouraging physicians from pursuing therapy titration. Other frailty tools, such as the Fried score or Edmonton Frailty Scale, are more comprehensive but less practical in non-geriatric settings.

Celutkiene, *et al*.[26] showed that guideline-directed rapid titration improves quality of life in a general population. A recent review reports that, in frail patients, HF interventions (therapeutic and rehabilitative) produce superior gains in quality of life and physical function,[27] but we did not evaluate it in our study.

Looking ahead, closer collaboration between cardiologists and geriatricians will be essential to address the specific needs of elderly patients with HFrEF. In fact, half of our cohort consisted of frail or pre-frail patients. Improving the classification and routine assessment of frailty may help tailor therapeutic strategies and reduce the impact of clinical inertia, which remains a major barrier to optimal care. Importantly, in this multimorbid population, quality of life and functional outcomes may represent more meaningful endpoints than mortality alone, and should therefore be prioritized in future research and clinical practice.

Limitations

This study has several limitations. Its observational, single-center design and short inclusion period resulted in a relatively small sample size with missing data at 3-month follow-up. The relatively small sample size, related to the focus on elderly patient, limits statistical power; therefore, the findings should be considered hypothesis-generating rather than confirmatory. Moreover, as the study was conducted in a tertiary expert center with a dedicated HF team, the findings may not be generalizable to other settings. Accordingly, the limiting factors and prognostic predictors identified here should be considered exploratory. Dedicated interventional studies are warranted to confirm these results.

Conclusion

An ITP for HFrEF therapy appears feasible and relatively safe in elderly patients. The development of joint cardio-geriatric care, combining frailty assessment and individualized management, should be encouraged, as should evaluation of its impact on quality of life and long-term outcomes.

STATEMENTS

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Disclosures

Artificial intelligence (AI) was used solely to assist with English translation; all scientific content, analyses, and interpretation were performed by the authors.

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