Comparison of 18-Month Outcomes of Ambulatory Patients With Reduced (≤40%) Left Ventricular Ejection Fraction Treated in a Community-Based, Dedicated Heart Failure Clinic Versus Treated Elsewhere

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We sought to examine the management and outcomes of ambulatory patients with heart failure and reduced ejection fraction in a community-based, dedicated clinic. Patients with left ventricular ejection fraction (LVEF) ≤40% were actively solicited to attend a community-based, dedicated clinic. Eligible patients who chose to decline constituted our control group. Of 552 patients with LVEF ≤40% (median age 73 years and median LVEF 35%), 304 (55%) agreed to attend the clinic. Patients with worse New York Heart Association class were more likely to attend the clinic (odds ratio 2.07 [1.45, 2.95], p <0.001), whereas women were more likely to decline (odds ratio 0.63 [0.42, 0.93], p <0.022). During 18 months of follow-up, patients in the dedicated clinic significantly improved their functional capacity (56% New York Heart Association 3 to 4 at baseline vs 27% at follow-up, p <0.001) and LVEF (35% [interquartile range 25, 35] at baseline vs 35% (interquartile range 30, 40) at follow-up, p <0.001). In comparison with patients managed routinely, patients treated in a dedicated clinic achieved better guideline-recommended pharmacological treatment (65% vs 85% receiving β blockers, p <0.001, 65% vs 82% receiving renin-angiotensin inhibitors, p = 0.0006, 31% vs 45% receiving mineralocorticoid receptor antagonists, p <0.001). During follow-up, electrical device implantation was similar (6% vs 7% of dedicated-HF-clinic patients, p = 0.700). Furthermore, overall survival was better in patients treated in the clinic (log rank p = 0.0006), even after censoring the first 4 months to account for potential bias (log rank p = 0.0232). In conclusion, management in a community-based, dedicated clinic compared with routine management was associated with augmented guideline-recommended treatment and improved survival.
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In an attempt to improve care for heart failure (HF) patients, dedicated clinics have been established worldwide.[1−4] However, reports regarding dedicated HF clinics are by and large descriptive, rather than comparative, and often include heterogeneous HF populations and heterogeneous practice settings.[1,5] Furthermore, it remains to be determined whether the augmented therapy in dedicated HF clinics is translated into a survival benefit in HF with reduced ejection fraction (HFrEF).[1,6] Therefore, we sought to investigate whether the management of ambulatory HFrEF patients in a community-based, dedicated HF clinic is associated with improved guideline-recommended pharmacological therapy and midterm survival, as compared with patients who elect to pursue routine management.

Methods

The electronic records of all patients >18 years old insured by the largest health care management organization in Israel ("Clalit" Health Services) in a designated district (n = 115,739 patients) were screened for the documented diagnosis of LVEF ≤40%. Patients >85 years were excluded. In collaboration with the general practitioners in the district and under the auspices of the district management, all eligible patients were actively solicited by a dedicated nurse by phone and/or written correspondence to attend a dedicated HF clinic within their community, with no additional payment required. Eligible patients that declined remained at the follow-up and management of either a general cardiology clinic and/or their family physician and constituted our control group (categorized as "routine management"). The prespecified study follow-up was 18 months (May 1, 2016 until October 31, 2017).

In the first visit, the patients were seen by a certified HF specialist, and those who were suitable were admitted to the titration program. The patient was examined by a nurse/HF specialist every 2 weeks according to the European Society of Cardiology guidelines for the initiation and titration HF medications.[7] The doses of β-adrenergic blockers

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(BB), angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and sacubitril/valsartan were titrated each visit according to the heart rate, blood pressure, renal function, and electrolytes, aiming to achieve maximal recommended dose or maximal tolerated dose. Notably, sacubitril/valsartan was not yet widespread available at the onset of the study.

The heart function was re-evaluated by echocardiography, and according to the LVEF, electrocardiographic parameters, and functional status, cardiac resynchronization therapy (CRT), and/or implantable cardioverter defibrillator (ICD) implantations were considered.

Clinical, pharmacological, and laboratory data of all patients at baseline and at the end of follow-up were extracted from the unique electronic medical records system of Clalit, as previously described.[8] Pharmacological and nonpharmacological management were at the complete discretion of the attending physician. LVEF was estimated visually by transthoracic or transesophageal echocardiography. Mortality during follow-up was determined for all patients through the Israeli National Population Registry. This study complies with the Declaration of Helsinki, that the local Institutional Review Board approved the research protocol

This study's primary end point was all-cause survival and the secondary end points were the use of guideline-recommended therapies and the proportion of patients achieving guideline-recommended doses at last follow-up versus baseline.

The statistical analysis for this paper was generated using SAS Software, Version 9.4. Continuous variables were presented by medians and interquartile range and categorical variables were presented as percentage. The Student's *t* test was used to compare the value of normally distributed continuous variables between study groups. The Wilcoxon test was used for non-normally variables and the Fisher's exact test was used for categorical variables. Univariate and multivariate odds ratios were evaluated by logistic regression. The Kaplan Meier model was used for overall survival. Landmark analysis, with a 4-month time point, was used to address the problem of immortality bias. For this survival model, patients with less than 4 months of follow-up were excluded. A 2-sided p value <0.05 was used for declaring statistical significance.

Results

We prospectively identified 552 patients who fulfilled our inclusion and exclusion criteria, of whom 304 (55%) accepted our proposal to attend a community-based, dedicated HF clinic. Patients' baseline characteristics are presented in Table 1. The majority of patients attending our dedicated HF clinic were males with a median age at presentation of 73 years (25th, 75th interquartile range of 65, 78). Patients attending the dedicated HF clinic had significantly worse HF functional status yet similar baseline LVEF compared with patients managed routinely. They were more likely to have had previous CRT or ICD implantations and influenza vaccinations. Multivariable logistic regression analysis (Table 2), demonstrated that worse HF functional status (NYHA class 3 to 4) was independently associated with acquiescence to management in a dedicated HF clinic. Women were more likely to decline.

The use of HF-targeted pharmacological treatment at baseline was similar between the study groups (Figure 1),

Table 1
Baseline characteristic of patients with heart failure with reduced ejection fraction treated in a dedicated heart failure clinic versus routine management

Variable	Management in a dedicated heart failure clinic		p value
	No (n = 248)	Yes (n = 304)	
Age (years)	73 (65, 79)	73 (65, 78)	0.978
Women	27%	19%	0.024
Body mass index (m^2/Kg)	26 (24, 30)	27 (25, 30)	0.083
Prior coronary artery disease*	69%	75%	0.085
Hypertension	77%	74%	0.375
Diabetes mellitus	54%	57%	0.606
Atrial fibrillation	21%	22%	0.917
New York Heart Failure functional class 3 or 4	33%	56%	<0.001
Estimated left ventricular ejection fraction (%)	35 (27, 40)	35 (25, 35)	0.195
Systolic blood pressure (mm Hg)	122 (113, 132)	120 (110, 130)	0.015
Heart rate (beats/min)	70 (65, 78)	72 (64, 78)	0.689
Estimated glomerular filtration rate (ml/min)†	65 (46, 83)	65 (48, 85)	0.845
Sodium (meq/L)	140 (138, 142)	140 (138, 142)	0.486
Potassium (meq/L)	4.6 (4,3, 4.9)	4.6 (4.3, 4.9)	0.899
Hemoglobin (g/dL)	13 (12, 14)	13 (12, 14)	0.794
Prior device implantation‡	30%	39%	0.034
Prior yearly influenza vaccination	63%	73%	0.013

Data are presented as medians (25th, 75th quartiles) or as percentages, as appropriate.

* Significant coronary artery disease in angiography.

† Estimated glomerular filtration rate- based on the Cockcroft-Gault formula

‡ Device implantation included implantation of an implantable cardioverter defibrillator, cardiac resynchronization therapy with or without a defibrillator, or pacemaker.

Table 2
Univariate and multivariate analyses of likelihood of patients with heart failure with reduced ejection fraction to be treated in a dedicated heart failure clinic

Variable	Univariate		Multivariate	
	Odds ratio (95%CI)	p value	Odds ratio (95%CI)	p value
Age	1.00 (0.98, 1.02)	0.978	1.00 (0.98, 1.03)	0.546
Women	0.63 (0.42, 0.93)	0.022	0.59 (0.36, 0.95)	0.028
New York Heart Association class 3-4 vs 1-2	2.07 (1.45, 2.95)	<0.001	2.27 (1.54, 3.37)	<0.0001
Documented coronary artery disease	1.34 (0.96, 2.03)	0.078	1.42 (0.93, 2.17)	0.951
Systolic blood pressure (mm Hg)	0.99 (0.08, 0.99)	0.029	0.99 (0.98, 1.00)	0.124
Diabetes mellitus	1.11 (0.79, 1.55)	0.550	1.03 (0.70, 1.52)	0.891
Estimated glomerular filtration rate (ml/min)	0.99 (0.99, 1.00)	0.844	1.00 (0.99, 1.01)	0.804
Left ventricular ejection fraction (%)	0.98 (0.96, 1.00)	0.195	1.01 (0.98, 1.04)	0.495
Prior electronic device implantation	1.50 (1.04, 2.16)	0.031	1.55 (0.99, 2.40)	0.053
Prior yearly influenza vaccine	1.59 (1.11, 2.29)	0.011	1.45 (0.96, 2.19)	0.081

except for lower doses of ACE-Is/ARBs at baseline in the group of patients attending the dedicated HF clinic (Figure 2). Sacubitril/valsartan was not yet available at the onset of the study. However, at the end of follow-up, more patients treated in the dedicated HF clinic received BB, renin-angiotensin inhibitors (either ACE-Is, ARBs or sacubitril/valsartan) and MRAs, as compared with patients managed routinely (Figure 1). These differences were mainly driven by a decrease in the use of BB, renin-angiotensin inhibitors and MRAs in patients managed routinely during study follow-up. Notably, in the dedicated HF group, the use of ACE-Is/ARBS decreased at the expense of increased use of sacubitril/valsartan, and thus the proportion of patients with inhibition of the renin-angiotensin axis remained stable. Furthermore, a greater proportion of patients attending the dedicated HF clinic achieved the maximal recommended doses of BB and ACE-Is/ARBs at the end of follow-up, as compared with patients managed routinely (Figure 2). Furthermore, more patients attending the dedicated HF clinic versus routine management were vaccinated for influenza during study follow-up (79% vs 69%, p = 0.008). Study groups were similar in the rates of patients that underwent electrical device (CRT alone or CRT with ICD, or ICD alone) implantation (6% of patients managed routinely vs 7% of patients treated in the dedicated-HF clinic, p = 0.700).

Hemodynamic and laboratory parameters of study patients at 18 months of follow-up are presented in Table 3. Kidney function and serum potassium levels were comparable. The systemic blood pressure at follow-up was significantly lower in patients treated in the dedicated HF clinic. A follow-up echocardiography exam was performed in 32% of patients managed routinely and in 80% of patients in dedicated HF clinics (p <0.001). Patients treated in a dedicated HF clinic improved both their LVEF and NYHA functional class compared with their baseline status (median LVEF at the end of follow-up 35% [interquartile range 30, 40] vs LVEF 35% [interquartile range 25, 35] at baseline p <0.001; proportion of patients with NYHA class 3 to 4 at the end of follow-up 27% vs 56% at baseline, p <0.001).

We further analyzed our data using only patients whom were followed by a general cardiologist as our control group (n = 180; Supplementary Tables 1 and 2). Again, patients with worse NYHA class were more likely to attend the dedicated HF clinic and women were more likely to decrease. At the end of follow-up, we noted greater use of BB and a nonsignificant trend for greater use of MRAs in patients treated in a dedicated HF clinic, primarily because of a decrease in use of these drugs in the subgroup treated in a general cardiology clinic (Figure 1). Furthermore, patients treated in a dedicated HF clinic were significantly more likely to achieve the maximal recommended doses of BB and ACE-Is/ARBs at the end of follow-up compared with patients treated in general cardiology clinics (Figure 2). Follow-up echocardiography exam was performed in only 36% of patients treated in general cardiology clinics. No significant differences were noted in the proportion of patients who underwent implantation of devices or influenza vaccinations between these 2 groups (data not shown).

The unadjusted cumulative incidence of mortality of patients attending the dedicated HF clinic was significantly lower compared with patients managed routinely (Figure 3). However, in order to partially preclude a potential mortality bias, whereby patients with life-threatening co-morbidities elected not to attend the dedicated HF clinic, we further excluded patients who died within 4 months of inclusion into the control or study subgroups or had less than 4 months of follow-up (Figure 3). Nevertheless, survival was better for patients attending the dedicated HF clinic. In addition, we analyzed the cumulative incidence of mortality using only patients attending general cardiology clinics as our control group (Supplementary Figure 1). A similar, yet nonsignificant trend was noted. Of interest, in all survival analyses, the graphs comparing the 2 groups continued to separate over time.

Discussion

This study provides new insights into the characteristics and care-patterns of outpatients with HFrEF treated in a community-based, dedicated HF clinic, by comparing their midterm outcomes to those of patients that elected to be managed either routinely or by a general cardiology clinic. We found that although all financial constraints were eliminated and services were offered within the community, patients with better HF functional status and women were more likely to decline management in a dedicated HF clinic. Furthermore, our findings demonstrate that treatment

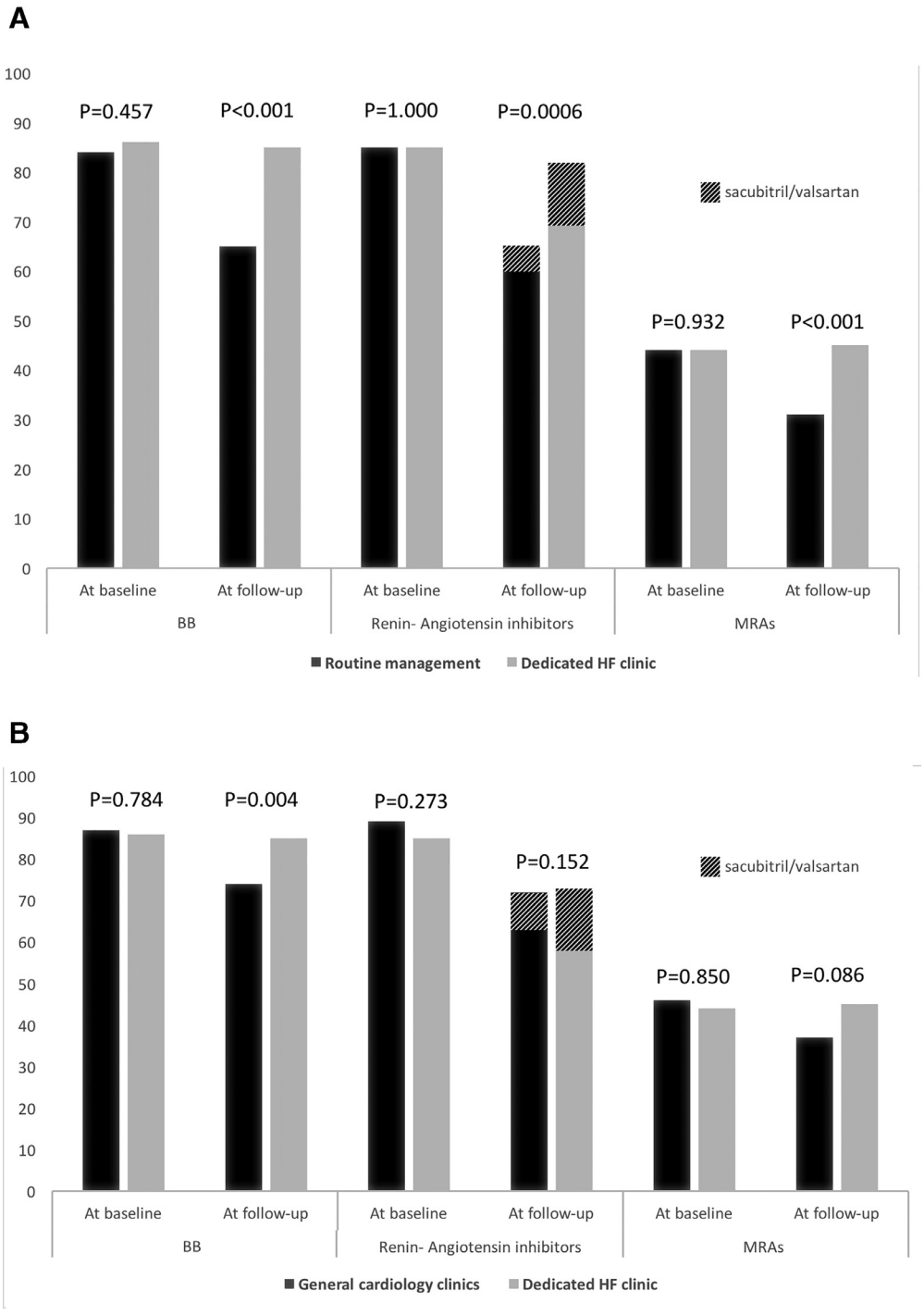
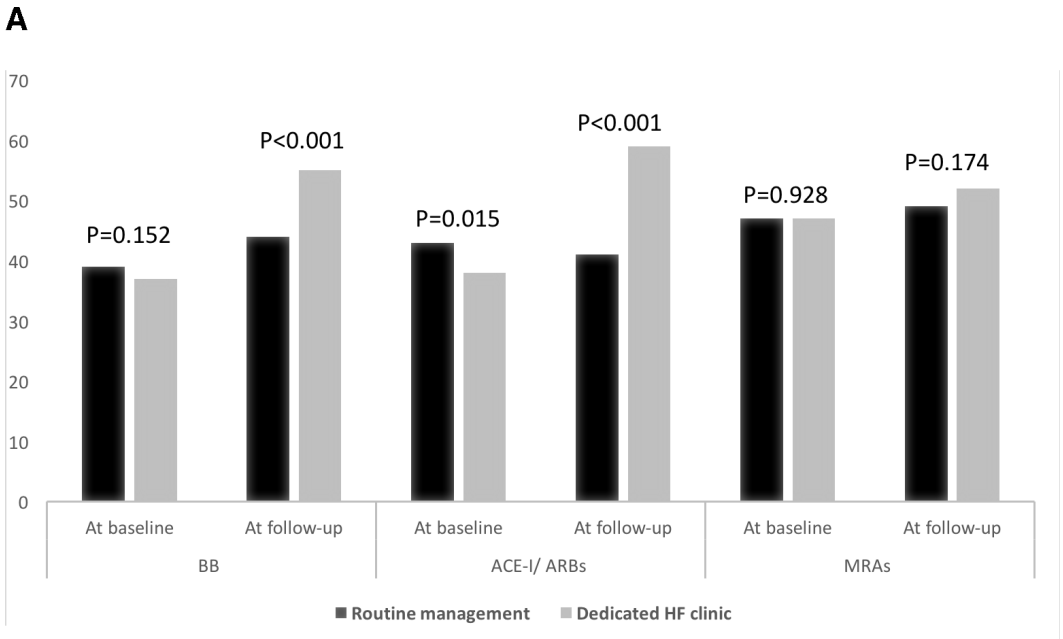


Figure 1. The proportion of patients receiving HF-recommended medications* at baseline and during follow-up. Comparison of patients managed in a dedicated HF clinic versus overall routine management (A) or specifically general cardiology clinics (B).
Data are presented as percentages.
*Sacubitril/valsartan was not widespread available in the beginning of the study, thus, use of renin-angiotensin inhibitors at baseline included only the use of ACE-I/ARBs, while at follow-up sacubitril/valsartan was added.

in a dedicated HF clinic significantly improved patients' functional capacity and LVEF, most probably owing to the achievement of more optimal guideline-recommended pharmacological treatment. Most importantly, we witnessed improved midterm overall survival in patients with HFrEF treated in a dedicated HF clinic.

The vast majority of contemporary evidence regarding HF outpatient management is derived from the Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting study,[3] which evaluated the effects of practice-specific performance improvement initiatives and demonstrated improvements both in adherence to



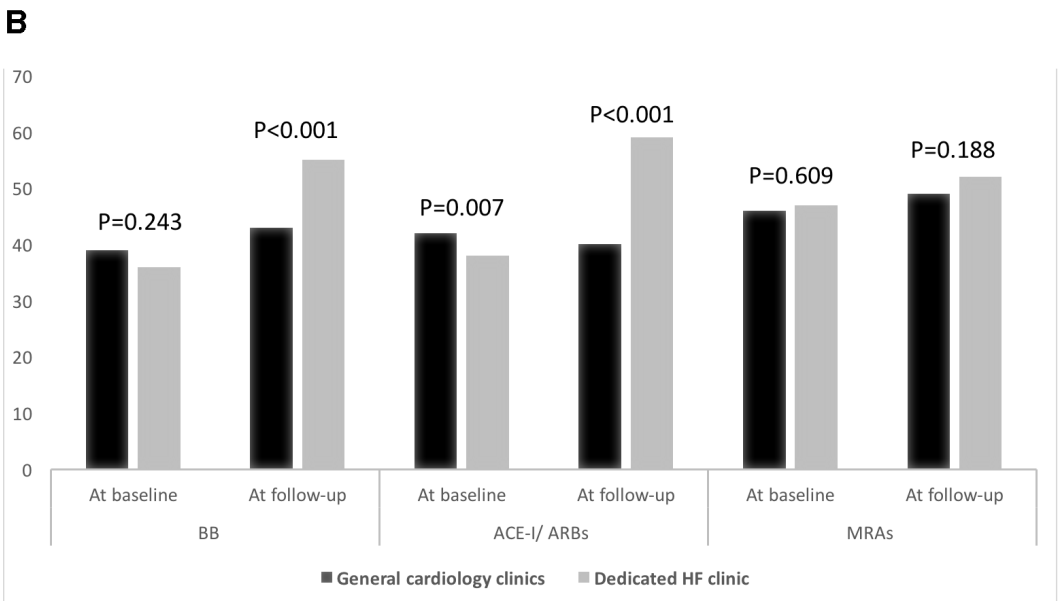


Figure 2. Proportion of maximal HF-recommended doses* at baseline and during follow-up among patients attending a dedicated HF clinic versus routine management (A) or specifically general cardiology clinics (B).
Data are presented as percentages.
*Data regarding sacubitirl/valsartan are not presented due to small sample size.

Table 3
Midterm parameters of patients with heart failure with reduced ejection fraction treated in a dedicated heart failure clinic versus routine management

Variable	Management in a dedicated heart failure clinic		p value
	No (n = 248)	Yes (n = 304)	
Body mass index (m^2/Kg)	26 (24, 30)	27 (25, 31)	0.110
Systolic blood pressure (mm Hg)	120 (114, 131)	120 (108, 130)	0.001
Heart rate (beats/min)	70 (64, 78)	69 (62, 76)	0.149
Estimated glomerular filtration rate (ml/min)	62 (45, 80)	59 (41, 78)	0.113
Sodium (meq/L)	140 (138, 142)	140 (138, 142)	0.704
Potassium (meq/L)	4.6 (4.3, 4.9)	4.6 (4.4, 4.9)	0.503
Hemoglobin (g/dL)	13 (12, 14)	13 (12, 14)	0.636

Data are presented as medians (25th, 75th quartiles).

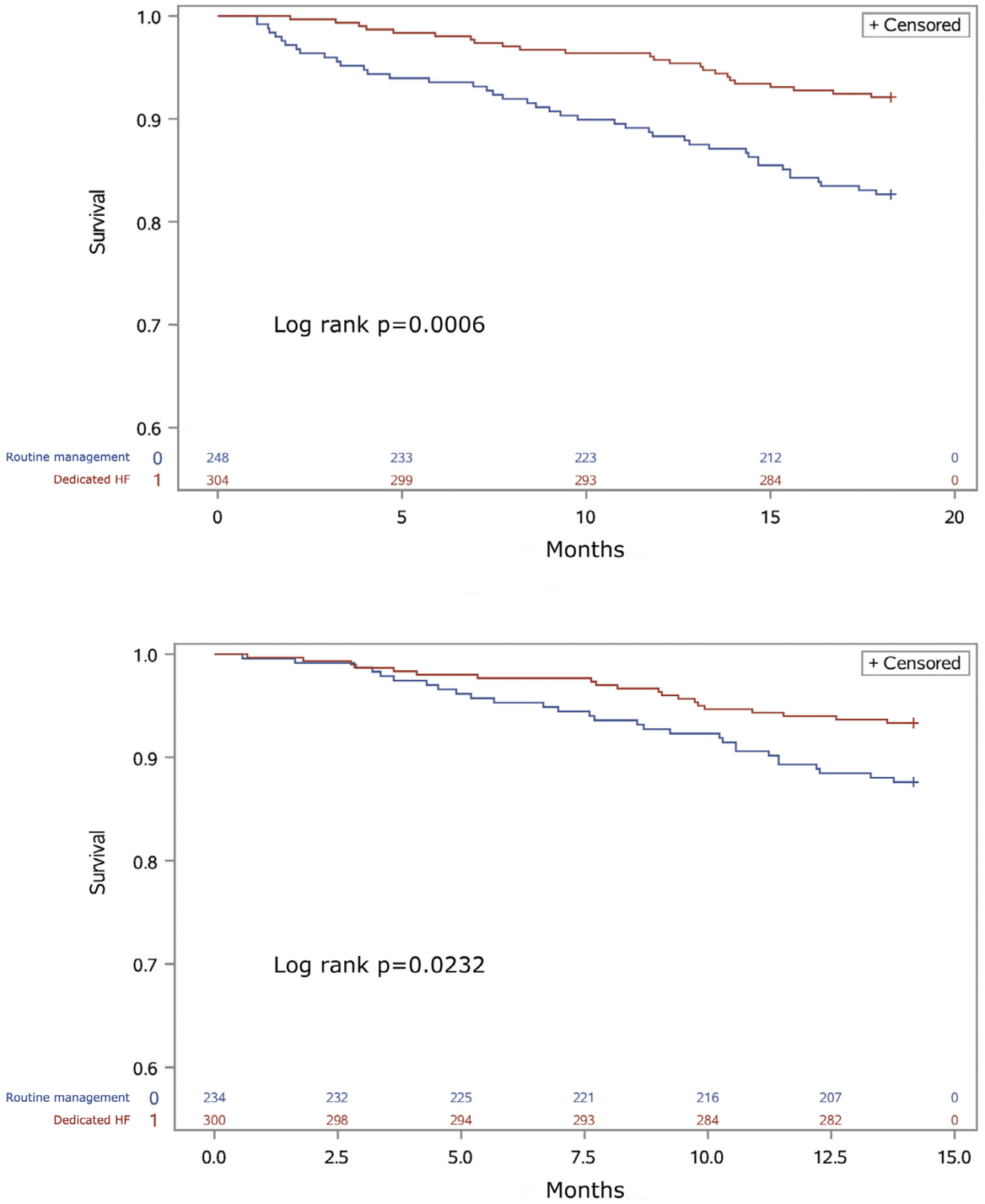


Figure 3. Midterm survival of patients attending a dedicated HF clinic versus routine management.
Kaplan-Meier estimates of probability of survival among patients attending a dedicated HF clinic versus routine management from the beginning of the study follow-up (A) or censoring for the four first months of study follow-up (B).

guideline-recommended therapies and LVEF.[9] However, one third of the participating cardiology practices in the Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting cohort were affiliated to an academic center or university setting, and less than half had a specialized HF clinic in the practice.[3] Moreover, outcome data were either descriptive or comparative to baseline status. Other contemporary evidence, by and large derived from dedicated HF clinics that were either university-affiliated or within tertiary-referral centers, described a decrease in the rates of acute HF decompensation, improvement in the quality of life, and a reduction in the need of in-hospital admissions.[6,10−13]

Our study is unique due to its prespecified patient selection and comparative design. First, our intervention group included real-life "all-comer" outpatients with HfrEF, who did not require a general practitioner referral or previous hospitalization to be included in the cohort. Moreover, the dedicated HF clinic model was community-based, and no additional payment was required from patients who chose to attend it, partially eliminating possible selection bias based on economic status. Second, this is the first comparative study, to our best knowledge, that analyzed the management and outcomes of HFrEF patients treated in dedicated HF clinics versus general cardiology clinics.

We found that during follow-up, more patients treated in the dedicated HF clinic received HF-recommended pharmacological treatment compared with patients managed routinely. Of interest, these differences were primarily due to a decrease in the use of these medications in the latter group. Although the decision to cease use of these drugs may, in fact, reflect a deterioration of the patients' HF status with hemodynamic compromise or worsening kidney function, it may also reflect less determination to reinstitute the use of these drugs after overcoming those transient difficulties. In contrast, the use of these drugs did not decrease over time in the group of patients managed in the dedicated HF clinic. Furhtermore, management of patients in the dedicated HF clinic was associated with achievement of higher target doses of BB, ACE-Is and ARBs, as previously shown by others.[14,15] The achievement of higher HF target doses is an established measure for improved clinical outcomes.[15−18] Moreover, the uptake of sacubitril/valsartan into clinical practice, only recently introduced yet universally available to all patients insured by "Clalit" and strongly advocated by recent guidelines,[7] was more efficient in patients treated in a dedicated HF clinic. Finally, this is the first study that demonstrates benefit in managing HFrEF patients in a dedicated HF clinic versus general cardiology clinics.

In the majority of previous studies, mortality was either not reported or unaffected,[1] but findings from studies focusing on in-hospital outpatient clinics did show a survival advantage for dedicated HF clinics over routine management.[6,19] Our data revealed a significant survival benefit for patients treated in a community-based, dedicated-HF clinic compared with patients treated routinely. A similar trend was evident when we compared the dedicated HF group to the subgroup managed in general cardiology clinics. In this subgroup analysis, the survival curves continued to separate during follow-up, possibly indicating an impact on survival that was either too early to discern or that the cohort size was underpowered to detect significant differences in survival. This salutary trend may be the result of both the higher adherence to guideline-recommended medical and invasive treatments and to the improvement of LVEF, all of which are established prognostic elements in patients with HFrEF.[20−22]

This study has several inherent limitations. The data analysis was retrospective, even though the data were captured prospectively. Thus, unmeasured variables may have impacted the results. We may also have missed HF patients whose LVEF was not recorded in the electronic records. Second, this study may have suffered from immortality bias. We attempted to partially address this bias in the survival analysis by censoring the first 4 months of initial solicitation, to account for patients who were too ill to attend the dedicated clinic. Third, this study is single-centered and the results may not apply to other outpatient community HF clinics. Fourth, it was not possible to distinguish between patients for whom dose titration was attempted but unsuccessful because of intolerance versus patients for whom no attempts to titrate medication doses were made. Nonetheless, these results reflect real-world management of HFrEF patients. Fifth, we lack data on the brain-natriuretic peptide levels of our patients during follow-up. However, a recently published study that used a strategy of NTpro-brain-natriuretic peptide-guided therapy was not more effective than a usual care strategy in improving outcomes of HFrEF patients.[23] Sixth, since we compared a group of patients willing to attend the HF clinic versus a group who declined to do so, this study may be fraught by a selection bias. However, patients who attended our HF clinic were actually sicker in terms of HF than our control group. Last, we have no data regarding the cause of death in our cohorts.

Disclosures

The investigators have no conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.12.033.

1. Gustafsson F, Arnold JM. Heart failure clinics and outpatient management: review of the evidence and call for quality assurance. *Eur Heart J* 2004;25:1596–1604.
2. Hauptman PJ, Rich MW, Heidenreich PA, Chin J, Cummings N, Dunlap ME, Edwards ML, Gregory D, O'Connor C M, Pezzella SM, Philbin E. The heart failure clinic: a consensus statement of the Heart Failure Society of America. *J Card Fail* 2008;14:801–815.
3. Fonarow GC, Yancy CW, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN. Heart failure care in the outpatient cardiology

practice setting: findings from IMPROVE HF. *Circ Heart Fail* 2008;1:98–106.
4. Aspromonte N, Gulizia MM, Di Lenarda A, Mortara A, Battistoni I, De Maria R, Gabriele M, Iacoviello M, Navazio A, Pini D, Di Tano G, Marini M, Ricci RP, Alunni G, Radini D, Metra M, Romeo F. ANMCO/SIC consensus document: cardiology networks for outpatient heart failure care. *Eur Heart J Suppl* 2017;19:D89–d101.
5. Fonarow GC, Yancy CW, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, Mehra M, O'Connor CM, Reynolds D, Walsh MN. Improving the use of evidence-based heart failure therapies in the outpatient setting: the IMPROVE HF performance improvement registry. *Am Heart J* 2007;154:12–38.
6. Howlett JG, Mann OE, Baillie R, Hatheway R, Svendsen A, Benoit R, Ferguson C, Wheatley M, Johnstone DE, Cox JL. Heart failure clinics are associated with clinical benefit in both tertiary and community care settings: data from the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) registry. *Can J Cardiol* 2009;25:e306–e311.
7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;18:891–975.
8. Shachak A, Hadas-Dayagi M, Ziv A, Reis S. Primary care physicians' use of an electronic medical record system: a cognitive task analysis. *J Gen Intern Med* 2009;24:341–348.
9. Wilcox JE, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Heywood JT, Inge PJ, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Gheorghiade M. Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: findings from IMPROVE HF. *Am Heart J* 2012;163. 49-56.e42.
10. Mirra M, Vitulano G, Virtuoso N, Tufano N, D'Auria F, De Angelis S, Giudice R, Lambiase A, Gigantino A, Piscione F. Heart failure in a dedicated outpatient clinic: results after 58 month follow-up. can it be enough? *Transl Med UniSa* 2015;11:59–62.
11. Pacho C, Domingo M, Nunez R, Lupon J, Moliner P, de Antonio M, Gonzalez B, Santesmases J, Vela E, Tor J, Bayes-Genis A. Early postdischarge STOP-HF-clinic reduces 30-day readmissions in old and frail patients with heart failure. *Rev Esp Cardiol (Engl Ed)* 2017;70:631–638.
12. Gouya G, Hammer A, Elhenicky M, Neuhold S, Wolzt M, Hulsmann M, Pacher R. Benefit of specialized clinics for the treatment of patients with heart failure. *Eur J Intern Med* 2011;22:428–431.
13. Zuily S, Jourdain P, Decup D, Agrinier N, Loiret J, Groshens S, Funck F, Bellorini M, Juilliere Y, Alla F. Impact of heart failure management unit on heart failure-related readmission rate and mortality. *Arch Cardiovasc Dis* 2010;103:90–96.
14. Driscoll A, Srivastava P, Toia D, Gibcus J, Hare DL. A nurse-led uptitration clinic improves chronic heart failure optimization of beta-adrenergic receptor blocking therapy—a randomized controlled trial. *BMC Res Notes* 2014;7:668.
15. Gheorghiade M, Albert NM, Curtis AB, Thomas Heywood J, McBride ML, Inge PJ, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW, Fonarow GC. Medication dosing in outpatients with heart failure after implementation of a practice-based performance improvement intervention: findings from IMPROVE HF. *Congest Heart Fail* 2012;18:9–17.
16. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996;94:2807–2816.
17. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009;374:1840–1848.
18. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999;100:2312–2318.
19. Stromberg A, Martensson J, Fridlund B, Levin LA, Karlsson JE, Dahlstrom U. Nurse-led heart failure clinics improve survival and self-care behaviour in patients with heart failure: results from a prospective, randomised trial. *Eur Heart J* 2003;24:1014–1023.
20. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Nielsen OW, Zannad F, Tavazzi L. EURObservational research programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2013;15:808–817.
21. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;34:1404–1413.
22. St John Sutton M, Pfeffer MA, Moye L, Plappert T, Rouleau JL, Lamas G, Rouleau J, Parker JO, Arnold MO, Sussex B, Braunwald E. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. *Circulation* 1997;96:3294–3299.
23. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL Jr., Mark DB, Pina IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2017;318:713–720.