Biomarkers-based Personalized Follow-up in Chronic Heart Failure Improves Patient's Outcomes and Reduces Care Associate Cost

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Abstract

BACKGROUND

Heart failure (HF) is a major and growing medical and economic problem, with high prevalence and incidence rates worldwide. Cardiac Biomarker is emerging as a novel tool for improving management of patients with HF.

METHODS

This is a real-world, before-and after-intervention trial, that assesses the impact of a personalized follow-up procedure for HF on patient's outcomes and care associated cost, based on a clinical model of risk stratification and personalized management according to that risk. A total of 192 patients were enrolled and studied before and after an intervention. The primary objective was the rate of readmissions, due to a HF event, post-intervention compared to pre-intervention. Secondary outcomes compared the rate of ED visits and the number of patients who had reduced NYHA score pre and post-intervention. A cost- analysis was also performed on these data.

RESULTS

Admission rates significantly decreased by 41% after the intervention (total length of stay was reduced by 55%). The rate of ED visits was reduced by 55%. Thirty-one percent of patients had an improved functional class score after the intervention, whereas only 7.8% got worse. The overall cost saving associated with the intervention was €139,717.65 for the whole group over 1 year.

CONCLUSIONS

A personalized follow-up of HF patients led to important outcome benefits and resulted in cost savings, mainly due to the reduction of patient hospitalization readmissions and a significant reduction of care- associated costs, suggesting that greater attention should be given to this high-risk cohort to minimize the risk of hospitalization readmissions.

Introduction

Heart failure (HF) is a major and growing medical and economic problem, with high prevalence and incidence rates worldwide [1,2]. It has been estimated that 0.5–2.2% of the population of industrialized countries suffer from HF, affecting more than 26 million people around the world, and HF is a leading cause of hospitalization [3,4]. The economic burden of HF is estimated at US\$108 billion per annum [5]. Patients with HF who have been hospitalized once have elevated hospital readmission rates, with nearly one in four patients being readmitted within 30 days of discharge, leading to increased care costs and poor outcomes [6].

Whilst improvements in therapy have enabled patients to live with HF for longer [7], optimizing management of HF remains a challenge and still today readmission rates following HF hospitalization remain high [8]. The association between readmissions, poor outcomes and rising costs is greatest in the first year after discharge, suggesting a need for interventions that increase surveillance in the early post-discharge period [9]. Personalized management of HF patients could address some of the challenges, and cardiac biomarkers are

emerging as a novel tool in for improve HF care [10]. Major Guidelines give recommendations for the use of biomarkers for assessing the risk of readmission and identifying unaffected patients at risk for incident HF, but provide very little recommendation about the optimal methods and whether biomarkers can or should be used for guiding chronic heart failure with reduced-ejection-fraction (HFrEF) follow-up and monitoring [11,12].

On the other hand, people affected by HF experience different physical and mental complications due to the chronic and prolonged disease course which have a serious and negative impact on patient's health-related quality of life (QoL). Poorer health-related QoL correlates with increased hospitalization times and mortality rates as well as higher costs imposed on health systems, families, and patients [13]. QoL in heart failure patients is a key objective of management. Assessment of health-related QoL is recommended. However, there is a lack of clarity on the best method. Despite the use of validated health-related QoL assessments in clinical trials, their use in routine practice is yet to be widely adopted [14]. Conversely, functional assessment using New York Heart Association (NYHA) classification is standard procedure in the monitoring of heart failure patients. In accordance with that, the focus should be the concept of using health-related QoL as endpoint for therapeutic intervention in chronic diseases such as HF [15].

Our objective was to study and validate a new, real-world clinical practice approach for HF personalized follow-up based on cardiac biomarkers compared with regular care in our clinical setting. Secondly, evaluate the impact on reduction of hospitalization readmission rates, reduction in the rate of visits to the emergency department (ED), and improvements New York Heart Association (NYHA) Functional Classification scores. We also aimed to evaluate the effect of the intervention on HF care-associated costs in terms of cost-effectiveness.

Methods

Design and Setting:

We conducted a before-and after-intervention trial in chronic HF patients, to evaluate the impact in patient's outcomes and care associate cost of a new approach for personalize follow-up based on biomarkers risk stratification. It was conducted from the perspective of the Spanish healthcare system in a single academic center (Huelva University Hospital, Huelva, Spain), a 600-bed academic teaching hospital and tertiary care referral center, with all major clinical services. The Heart Failure Unit (HFU) is the referral unit for a population of 550,000 and sees approximately 1000 patients per year. The protocol was approved by the institutional review board, and a waiver of the requirement for a written consent from all participants was approved.

Participants:

A total of 192 patients were enrolled between June 2017 to 2018 (figure 1). The study included chronic HF patients, aged 18 years or over and with a reduced left ventricular ejection fraction (LVEF) of 40% or less. In summary, all patients with HF visiting the HFU clinics were consecutively included in the study. Diagnosis and management of HF was in accordance with international guidelines. The follow-up time for all the patients was 12 months before and 12 months after intervention. The follow-up protocol included a medical examination, completion of a patient questionnaire (including all relevant clinical variables, signs and symptoms, medication, NYHA score, use of cardiac resynchronization therapy [CRT] and devices such as

implantable cardioverter defibrillators [ICD]), blood testing, electrocardiogram (EKG or ECG), and drug treatment adjustments. Before the intervention, all patients were visited every 3 to 6 months according with their symptoms, no matter what their risk was and biomarkers were not used for follow up neither for stratifying risk.

Intervention:

We designed a specific intervention based on a personalized follow-up protocol according to a risk stratification score that included biomarkers as first line for risk asses monitoring. At the time of discharge NT-proBNP and high-sensitivity Troponin T (hs-TnT) levels were measured and then, patients were categorized into 3 different groups (low, medium and high risk) according with their risk of readmission calculated using the Barcelona Bio-Heart Failure Risk Calculator (BCN Bio-HF Calculator) [16,17]. BCN Bio-HF Calculator provides with good accuracy (AUC 0.83) the individual risk of hospitalization and all cause-death yearly, up to 5 years in chronic HF patients and incorporates conventional predictors factor as well as NT-proBNP and hs-TnT, that are highly accurate for cardiac malfunction. The calculator was developed with different models allowing its use with different biomarkers. In our study, we used the model that incorporated two biomarkers, NT-proBNP and hs-TnT. According to the risk stratification we developed a personalized follow-up protocol for each group. Quartiles of the total distribution were selected as cut-off points for the different groups, with follow-up at the HFU after discharge as follows:

- Low-risk patients (score <5%), follow-up at 90 days and 12 months.
- Medium-risk patients (score 5–15%), follow-up at 60 days and 6 and 12 months.
- High-risk patients (score >15%), follow-up in 30 days and 3 and 12 months.

Clinical outcomes:

The primary outcome compared the rate of readmission post-intervention with pre-intervention, due to a HF event, in the same period between 2017 and 2019.

Secondary outcomes compared the rate of ED visits and the number of patients who had reduced NYHA scores pre- and post-intervention.

Cost analysis:

The cost-effectiveness analysis was conducted from the perspective of the Spanish healthcare system, including categories of costs shown in Table 1. All costs were calculated by multiplying the unit cost for the resource use. The average cost of hospitalization was calculated as the number of patients in each NYHA class multiplied by the diagnosis-related group (DRG) cost for each class. The primary care visit unit cost of €78.45 was calculated according to methods used by Merino M et al. [18]. The cost of ED visits was calculated according to the unit cost to the specific DRG of €392.03. The medication unit cost was calculated using the Spanish healthcare prices for Huelva University Hospital in 2018, multiplying by the dose for each patient and calculating the mean in a 1-year period. Laboratory unit costs were calculated as an incremental cost of €14 associated with the cost of the biomarker used during the post-intervention period.

Quality adjusted life-years (QALYs) were calculated by assuming that each functional class has a constant utility function throughout the year, multiplied by 1 year (study period) [17]. The total QALYs were calculated as the sum of each functional class multiplied by the number of patients in that class. All costs were adjusted for inflation to reflect cost related to the year 2018 and excluding indirect costs. For the cost-effectiveness analysis, we considered a temporary analysis of 1 year. To test uncertainty, we used a non-parametric bootstrap method using the original un-transformed data set to generate an empirical distribution for the difference in mean costs, from which we can obtain the confidence interval around the sample mean estimated for costs. The 95% confidence interval for the mean cost in the two groups of patients was obtained non parametrically using the 5th and 95th percentiles from the distributions as reported in Table 2. We also conducted sensitivity analyses by subgroups. After determining the dominant strategy, we calculated the overall budget impact of using that. This estimation was weighed by the number of HF diagnostic in one year. To assess the budget impact, we simulate three different scenarios: the best case scenario involved that 100% of the HF were managed using the new approach, the intermediate-case scenario involved that 75% of the HF and the worst-case scenario where only 50% of the HF were managed according with the new approach.

Statistical analysis:

Sample size was determined based on detecting a difference between groups at 12 months with a power of 80% and a significance level of 5%, detected using a two-tailed t-test, and assuming a loss to follow-up rate of 25%. The rationale for this was based on data from previous studies related to the primary outcome. The sample size required was 143 patients in total, increased to 192 patients due to the expected dropout rate of 25%.

Distributions were examined using the Shapiro–Wilk test to ensure proper statistical evaluation. Continuous variables were expressed as the median with 95% confidence intervals (95% CI), except glomerular filtration, which was expressed as mean $\pm$ standard deviation (SD), and the categorical variables, which were expressed as a frequency (percentage, %) of the population. The differences among the categorical variables were analyzed using the chi-square test (χ^2), while the Kruskal–Wallis test was used to analyze the differences between independent continuous variables, except glomerular filtration. Significance levels less than 5% were considered significant. Statistical analyses of the data were performed using IBM SPSS software (version 22, SPSS Inc., USA).

Results

Study cohort

At the time of this analysis, 192 patients had been enrolled in this study with 1 year of follow-up (Figure 1). Table 3 shows the baseline characteristics of the study cohort. Overall, 79.7% of all patients were male, and the mean age ($\pm$ SD) was 64 ± 12 years. Common comorbidities included hypertension (69.3%), diabetes (37.5%), chronic renal failure (25.8%), chronic obstructive lung disease (20.3%), and atrial fibrillation (34.9%). Of those with heart disease, 50% had coronary artery disease, although a majority of patients (69.8%) had no HF hospitalizations in the year before enrollment. Most patients, 83.7% from Table 3 (NYHA I is 36.1% and NYHA II is 47.6%) were assessed as NYHA Class I or II, reflecting prevalently a mildly symptomatic HF cohort. We found levels of NT-proBNP of 984 [95%CI 393-2334] pg/mL, and hs-TnT levels of 15 [95%CI 8-27] ng/mL. We found

HF hospitalization readmission rates of 30.2% and 21.9% visited the ED during the 12 months prior to the intervention.

The subgroups analysis showed that the patients in the highest risk group were more likely to be older, had more comorbidities, and their heart disease was at a more advanced stage. We found levels of NT-proBNP of 599 [95%CI 244-1211] pg/mL, 2045 [95%CI 860-3664] pg/mL and 3494 [95%CI 1503-8541] pg/mL ($p<0.001$) and hs-TnT levels of 11 [95%CI 6-16] pg/mL, 24 [95%CI 17-40] pg/mL and 53 [95%CI 39-68] pg/mL ($p<0.001$) for the low, medium and high risk patients respectively.

For the low risk group 91.4% of the patients were in the lowest functional class (NYHA class I or II), 76.5% for the medium risk group and 50% for the high risk groups. No differences between groups were found in the LVEF either in the use of therapies included Angiotensin-receptor-neprilysin-inhibitor (ARNI), Angiotensin Converting Enzyme Inhibitor (ACEI)/Angiotensin Receptor Blocker (ARB) or beta-blockers (BB).

Clinical Outcomes

Primary outcomes

Table 3 compares the main outcome of rate of admission 30 days, 6 months and 12 months before and after the intervention, analyzing patients by risk groups. In the cohort of 192 patients, there were 78 admissions for HF (total Length of Stay [LOS] of 647 days) in the 12 months before the intervention. This decreased to 46 admissions after the intervention (total LOS of 295 days), a 41% reduction ($p<0.001$).

Of the total, 7.8% had been admitted at least once in the 30 days prior to the baseline visit, which reduced to 1% in the 30 days following the intervention ($p=0.002$). The respective proportions being admitted before and after intervention in the low-, medium- and high-risk groups were 5.1% and 0% ($p=NA$), 9.5% and 1.6%, ($p=0.125$), and 25% and 8.3% ($p=0.625$). Overall, a significant reduction was observed when comparing 6 months before (20.3%) and 6 months after intervention (6.3%) ($p<0.001$).

Of the 192 patients, 30.2% of the sample had been admitted at least once the previous year; after the intervention, this number decreased to 10.4% in a year ($p<0.001$). The respective proportions in the low-, medium- and high-risk groups before and after the intervention were: 22.2% and 5.1% ($p<0.001$); 38.1% and 14.3% ($p=0.125$); and 66.7% and 41.7% ($p=0.453$).

Secondary outcomes

The rate of visits in the ED also decreased after the intervention (Table 4a). In the 12 months before the study, the number of visits was 64, which decreased to 20 after the intervention, a reduction of 68.8% ($p<0.001$).

A marked functional improvement was observed after the intervention (Table 4b). In total, 31.1% of the patients improved at least one class in NYHA score, 61.6% remained the same, and 7.3% got worse. The number of asymptomatic patients also increased by 10%.

Costs analysis

Table 2 compares the total care associate cost and the specific components during the follow-up between the groups. The overall cost of applying the new follow-up intervention for the cohort of 192 patients was € 139,717 lower compared with standard care pre-intervention (Figure 2). We found a significant cost reduction in most of the categories considered. The most important cost reduction was related to costs associated with hospitalization, demonstrating a significant reduction of 78% ($p < 0.05$).

There was a reduction of 69% in the number of ED visits (reduction in total cost for the post-intervention group of €17,249 compared with the pre-intervention group), and there was a significant reduction in the costs associated with primary care visits and with medication. There was a corresponding incremental cost related to the use of biomarkers (€1,728) and HFU visits (€28,567).

Utilizing the personalized biomarker approach produced a total of 113.6 QALYs (95% CI 108.5 to 118.2) compared with 109.1 QALYs (95% CI 104.2 to 113.4) for regular care, an increment of 4.5 QALYs (95% CI 2.9 to 6.1). The new approach was dominant (both less costly and more effective). The sensitivity analysis indicates that the new approach is the most cost-effective decision (Figure 3).

The budget impact analysis showed a potential saving between €-704,028 per 1000 patient-years (p-y) (95% CI 1,141,654 to -273,829) when the saving per patient were translated to the overall patient population in the best-case scenario (100% of the HF patients conducted using our new approach), to €-352,014 p-y (95% CI -570,827 to -136,914) in the worst-case scenario (100% of the HF patients conducted using our new approach), with a medium-case scenario (50% of the HF patients conducted using our new approach) potential saving of €-528,021 (95% CI -856,240 to -205,371). Based on the 80,000 hospital admissions for HF that occur every year in Spain [18], the budget impact, considering only direct costs, could be between €-56,322,308 (95% CI -91,332,342 to -21,906,326) in the best-case scenario and €-28,161,154 (95% CI -45,666,171 to -10,953,163) in the worst-case scenario.

Discussion

Although a principal goal of HF management is to improve patient outcomes, few studies have evaluated the possibility of carrying out personalized management to improve them, as we did. The primary finding of this study is that a strategy of personalized follow-up based on cardiac biomarkers for patients with chronic HF and reduced LVEF was more effective than regular care in reducing the composite outcome of readmission rates. Significantly different results were seen in other clinical outcomes, including a reduction of ED visits and improvement in patients' NYHA classification during the monitoring period. There was also a significant reduction in the HF-associated cost using the personalized approach compared with the strategy used in regular care.

These results are comparable with the published literature; the 1-year incidence rate of readmission was reported at 14.5% among 12,440 chronic HF patients from different geographical areas [6]. A systematic review of different strategies for HF management found 6/19 trials demonstrated statistically significant reductions in HF readmissions with multidisciplinary management and personalized follow-up strategies [19]. The average reduction in readmission rates was 12.37% over 12 months' follow-up, varying between 2.71% and 17.81% [19,20]; differences between types of interventions were not found.

Although difficult to compare across studies, the reduction in hospitalization readmissions after 1 year of follow-up was substantially higher in this study (17–25% across risk groups). This may result from the focusing of resources on those patients at highest risk. We believe this study is the first to propose a personalized follow-up procedure based on the patient's risk, assessed in a real-world clinical scenario, and suggests that greater attention should be given to the high-risk cohort to minimize the risk of readmissions; given that most hospital readmissions are for non-HF reasons, a comprehensive medical treatment plan has been implemented.

As many as 77% of high-risk patients initially present to the ED [22], and close follow-up after discharge has been shown to decrease ED admissions [23,24]. Our results differ from these studies and show a significant reduction of 68.7% in ED admissions during the follow-up period. Although the majority of hospitalizations for HF begin in the ED, close outpatient follow-up and management has been proposed as a viable strategy to reduce readmissions.

We found a reduction in the percentage of patients in NYHA class III and an increasing number of patients in NYHA class I and II at follow-up, comparable with the results of Romano et al. ED [25] and other authors that found a significant improve in NYHA class after different interventions in patients with HFrEF [26]. NYHA class is recommended in all guidelines as a useful tool to assess the functional limitations imposed on a patient by their heart failure. In fact, NYHA functional class was the most dominant predictor among several somatic variables studied, without LVEF or duration of HF associated with a decrease in quality of life [27]. The results of the current study strongly support the current guidelines regarding NYHA class reduction as primary endpoint for therapeutically interventions in HF.

Our cost analysis results agree with those proposed by other groups; Lesyuk et al. [28] found that 44–96% of the direct costs of HF care are due to hospitalization, suggesting that reduction of readmission rates would reduce the direct cost associated with HF. Our study also reports a significant reduction in the cost related to emergency admission and primary care visits, which we believe are associated with better control of the patients after the intervention. The significant reduction in NYHA class could also contribute to the cost reduction; patients with NYHA IV have between 8 and 30 times higher healthcare costs than patients with NYHA II [29,30].

Data for the cost-effectiveness of biomarker-guided personalized outpatient management of HF patients are limited. Our cost-effective analysis showed that personalized follow-up was the dominant approach, with a potential saving of €-704,028.85 per 1000 p-y. Given the expected cost differential between serial biomarker monitoring and hospitalization for HF, even a modest reduction in admissions due to biomarker personalized follow-up could result in net cost savings. Biomarker personalized therapy has a high probability of being cost-effective in HF patients with reduced LVEF [30].

This study has several limitations. The data needs to be validated in a multicenter, randomized clinical trial. The model of care for HF is currently carried out according to local practices, where there is a large variability in the clinical management of patients. Our study only reflects the experience of a single hospital, and the analyses were conducted from the Spanish health system perspective, including pricing. General population data ranges were used in the sensitivity analyses to improve generalizability. Demonstrating the prices and

efficacy necessary for cost-effectiveness at each threshold makes our results relevant to other systems, and transferrable to clinical practice.

Conclusions

In conclusion, personalized handling in HF, with novel clinical strategies for optimizing treatment, improving outcomes, and reducing the cost in HF, is sorely needed. Our strategy of personalized follow-up based on cardiac biomarkers to optimize HF management represents a major new approach to achieve these goals.

Abbreviations

HF Heart Failure

HF_rEF heart failure with reduced-ejection-fraction

ICHOM International Consortium for Health Outcomes Measurement

ED Emergency department

NYHA New York Heart Association

HFU Heart Failure Unit

LVEF left ventricular ejection fraction

CRT cardiac resynchronization therapy

ICD implantable cardioverter defibrillator

ECK/ECG electrocardiogram

NT-proBNP N-terminal pro b-type natriuretic peptide

Hs-TnT Troponin T

BCN Bio-HF Calculator Barcelona Bio-Heart Failure Risk Calculator

AUC Area under the ROC Curve

DRG Diagnosis-related group

QALYs Quality adjusted life-years

CI Confidence intervals

SD standard deviation

ARNI Angiotensin-receptor-neprilysin-inhibitor

ACIE Angiotensin Converting Enzyme Inhibitor

ARB Angiotensin Receptor Blocker

BB Beta-blockers

Declarations

Ethics approval and consent to participate

The study is in accordance with Helsinki Declaration. Institutional ethics committee approval was obtained from the Huelva University Hospital, Research Ethics Committee . Participants gave their informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

JMG reports personal fees from Roche Diagnostics International Ltd during the conduct of the study. All other authors have nothing to disclose.

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Authors' contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Tables

Table 1: Categories of costs included in the analysis, per unit

	Cost (€)
Hospitalization cost	3,981.89
NYHA 1	2,900.76
NYHA 2	3,654.64
NYHA 3	4,426.22
NYHA 4	6,662.33
Primary care visits	78.45
Emergency Department visits	392.03
Heart Failure Unit visits	97.83
Medication cost	1.32
ACEI	0.09
ARA II	0.54
MRA	0.04
Ivabradine	0.36
Diuretics	0.03
Statins	0.13
Angiotensin receptor-neprilysin inhibitors	0.54
Biomarkers cost	14.00
NT-proBNP (pg/mL)	12.00
hs T-Troponin (ng/mL)	2.00

ACEI, Angiotensin-converting enzyme inhibitor; ARA, aldosterone receptor antagonist; MRA, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide

Table 2: Differences in total costs during the 12 months of follow-up for the pre-intervention and post-intervention groups by individual cost categories

Cost Categories	Pre-intervention (€, 95% CI)		Post-intervention (€, 95% CI)		Difference	
Hospitalization cost	276,240.59	[196,934.82, 376,573.91]	128,188.07	[60,774.36, 217,678.26]	-148,052.52	[-237,083.74, -104,020.22]
Primary Care Visits	4,550.10	[3,136.04, 6,276.00]	1,804.35	[941.40, 3,059.55]	-2,745.75	[-4,785.45, -1,019.85]
Emergency Department Visits	25,089.92	[16,465.26, 36,860.62]	7,840.60	[4,312.33, 12,152.93]	-17,249.32	[-29,794.28, -7,438.77]
Heart Failure Unit Visits	54,195.65	[52,120.64, 55,983.00]	82,762.83	[80,013.51, 85,954.66]	28,567.18	[23,680.63, 33,374.36]
Medication cost	26,207.00	[23,698.17, 28,864.29]	25,969.75	[23,622.44, 28,449.38]	-237.25	[-1,909.68, 1,335.90]
Total	386,283.26	[303,583.75, 487,853.96]	246,565.60	[177,569.86, 338,841.40]	-139,717.65	[-224,000.78, -63,958.01]

Table 3: Baseline characteristics of the study cohort, for associations between variables depending on the score groups

	Total (N=192)	Low-risk (n=117)	Medium-risk (n=63)	High-risk (n=12)	p value
Age (years)	65 [57–73]	60 [53–69]	72 [66–77]	73 [65–81]	<0.001
Gender (female)	20.3	23.9	14.3	16.7	0.292
Arterial hypertension	69.3	58.1	85.7	91.7	<0.001
Dyslipidemia	64.1	52.1	82.5	83.3	<0.001
Diabetes mellitus	37.5	25.6	54.0	66.7	<0.001
COPD	20.3	13.7	30.2	33.3	0.016
Chronic renal failure	25.8	13.0	42.9	58.3	<0.001
Previous atrial fibrillation	34.9	22.2	50.8	75.0	<0.001
LVEF	30 [27–36]	30 [28–36]	30 [28–36]	27 [25–32]	0.116
Ischemic etiology	50	40.2	65.1	66.7	0.003
Functional class					
NYHA 1	36.1	44.8	23.8	16.7	<0.001
NYHA 2	47.6	46.6	52.4	33.3	
NYHA 3	16.2	8.6	23.8	50.0	
ICD/CRT	12.0	5.1	20.6	33.3	0.001
Heart rate	61 [55-70]	60 [55-66]	63 [60-70]	64 [59-80]	0.107
NT-proBNP (pg/mL)	984 [393–2334]	599 [244–1211]	2045 [860–3664]	3494 [1503–8541]	<0.001
hs T-Troponin (ng/mL)	15 [8–27]	11 [6–16]	24 [17–40]	53 [39–68]	<0.001
Glomerular filtration (mL/min/1.73 m ²)	76.07±27.75	86.36±23.66	62.54±22.59	46.75±38.50	<0.001
Sodium (mEq/L)	141 [140–143]	141 [140–143]	142 [141–144]	139 [138–141]	0.005
ACEI/ARB	60.4	62.4	58.7	50.0	0.667
ARNI	38.0	35.9	39.7	50.0	0.598
Betablockers	95.8	97.4	95.2	83.3	0.064
MRA	78.1	76.1	82.5	75.0	0.584

Diuretics	67.7	47.0	100.0	100.0	<0.001
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Data are presented as median [95% CI] for continuous variables and percentages for categorical variables. ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICT, implantable cardioverter defibrillators; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide

Table 4: Rehospitalization rates, rate of admission from the emergency department (ED), and NYHA functional classification scores, 30 days, 6 months and 12 months pre- and post-intervention

	Sample size	Pre-intervention	Post-intervention	p value
30-days admissions (%)	All (N=192)	7.8	1	0.002
	Low risk (n=117)	5.1	0	NA
	Medium risk (n=63)	9.5	1.6	0.125
	High risk (n=12)	25	8.3	0.625
6-months admissions (%)	All (N=192)	20.3	6.3	<0.001
	Low risk (n=117)	15.4	1.7	<0.001
	Medium risk (n=63)	23.8	11.1	0.096
	High risk (n=12)	50	25	0.453
12-months admissions (%)	All (N=192)	30.2	10.4	<0.001
	Low risk (n=117)	22.2	5.1	<0.001
	Medium risk (n=63)	38.1	14.3	0.003
	High risk (n=12)	66.7	41.7	0.453

Table 5.a Change in ED visits pre- and post-intervention (total and by subgroups)

		Pre-intervention	Post-intervention	p value
30-day ED visits (%)	Total (N=192)	4.7	0	NA
	Low risk group (n=117)	1.7	0	NA
	Medium risk group (n=63)	7.9	0	NA
	High risk group (n=12)	16.7	0	NA
6-months ED visits (%)	Total (N=192)	12.5	2.1	<0.001
	Low risk group (n=117)	7.7	0.9	0.021
	Medium risk group (n=63)	15.9	1.6	0.012
	High risk group (n=12)	41.7	16.7	0.375
12-months ED visits (%)	Total (N=192)	21.9	7.3	<0.001
	Low risk group (n=117)	12.8	3.4	0.013
	Medium risk group (n=63)	31.7	9.5	0.007
	High risk group (n=12)	58.3	33.3	0.453

Table 5.b Change in functional class (NYHA) pre- and post-intervention

(total and by subgroups)

	Improved (% , 95% CI)	No change (% , 95% CI)	Worse (% , 95% CI)
Total	31.07 (24.71, 37.78)	61.58 (54.94%, 67.86)	7.34 (3.87, 11.3)
Low	28.70 (20.72, 37.28)	65.74 (56.91, 73.69)	5.56 (1.9, 10.48)
Medium	37.93 (26.15, 50)	53.45 (41.43, 65.08)	8.62 (1.75, 16.67)
High	22.22% (0, 55.6)	55.56 (20, 90)	22.22 (0, 50)

*Confidence intervals were calculated with n = 1000 and 95% confidence level.

Figures

Figure 1

Flow of patients through the study

Figure 2

HF cost according to groups. Values are expressed in euros.

Figure 3

One thousand bootstrap estimates of the differences in mean cost and mean (quality adjusted) survival time between pre- and post-intervention. The cost-effectiveness plane represents the incremental costs and effects of the intervention compared to regular care. The origin represents the comparator treatment, in this case non personalized follow up management. If the new intervention lies to the right of the origin it is more effective (i.e., it has more QALYs than those with regular care), or if it lies to the left of the origin it is less effective. If it lies above the x-axis then it is more costly than B, and vice versa.