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Medical Inertia in the Optimization of Heart Failure Treatment after Discharge and its Relationship to Outcome

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Abstract

Background: After discharge, patients with Acute Heart Failure (AHF) have a high risk of early re-admission and death. Many patients are discharged early before treatment has been optimized. By using a multicenter cohort of AHF patients, we analyzed changes in evidence-based HF medication between admission, discharge and early follow-up as well as their links to mortality.

Methods: Clinical data and medications were collected during hospitalization. Changes in medication during the 3 months following discharge as well as the rate of all-cause mortality at one year were analyzed.

Results: Among survivors at 3 months, 275 patients with LVEF ≤ 40% were included (age 72 ± 14 y). Between admission and discharge, usage of angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) and beta blocker (BB) increased by 19 to 20% and MRA by 8%. At discharge, ACE-I or ARB were prescribed in 80% of cases with the mean dose reaching 36 ± 31% of target dose, BB in 70% with the mean dose of 27 ± 51% of the target dose, mineraloreceptor antagonists (MRA) were prescribed in 23% and diuretics in 88% cases. Three months after discharge, there were few changes in medications. Start in ACE-I or ARB, beta-blockers and MRA was performed in 3 to 7% while cessation was performed in 5 to 6% cases. Changes in doses were observed in about 25% cases. usage of BB and Ace ORARB >/ % of target dose at 3 months shows a tendency to deusage montality [HR=5,2999;95%ic1,7369-16-1722; p=0,0635].

Conclusion: Our data points out inertia in optimization of evidence-based HF medications after discharge and focus on potential explanations of such inertia. Medical ineatia have a potential impaction on outcomein heart failure.

Keywords: Heart failure; Medical treatment; Inertia; Outcome

Abbreviations: ACE-I: Angiotensin Converting Enzyme Inhibitor; AHF: Acute Heart Failure; ARB: Angiotensin Receptor Blocker; BB: Beta-Blocker; COPD: Chronic Obstructive Pulmonary Disease; LVEF: Left Ventricular Ejection Fraction; HF-REF: Heart Failure with Reduced LVEF; ICD: Implantable Cardiac Defibrillator; MRA: *Mineralocorticoid Receptor Antagonist*

Introduction

Heart failure (HF) is a major and increasing cause of morbidity and mortality [1-4]. The risk of cardiac events is particularly high just after discharge. Over the last decades, major advances have occurred in the medical treatment of patients with HF and reduced left ventricular ejection fraction (LVEF), including ACE-inhibitors (ACE-I), Angiotensin receptors blockers (ARB), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), ivabradine and recently LCZ696. This has led to the production of robust guidelines to support physicians in the clinical decision-making of HF patients with reduced LVEF [5,6]. Some surveys have noted that many of these patients do not receive evidence-based treatment at all, or do receive treatment but without optimal dosages, despite physicians being increasingly encouraged to apply the guidelines to their practice [7-10]. The reasons are numerous, including the patient's condition (age, comorbidities, adherence) as well as the physician's choices (ignorance of the guidelines, misgivings about new treatment, focus on patient symptoms rather than reduction of mortality), and access to health care [9-14]. However, data on changes in treatment over follow-up are scarce, particularly during the early follow-up of patients after an acute HF event. In order to bridge this gap of information by using a representative sample of AHF patients with reduced LVEF from a nationwide survey, we analyzed the usage of evidence-based HF medications on admission and discharge

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as well as the changes at 3 months and subsequent links to mortality after one year.

Methods

We analyzed data from the nationwide survey known as OFICA (NCT01080937). Methods and the main results of this survey have been described in a previous paper [15]. Briefly, this survey included all hospitalized patients with a confirmed diagnosis of AHF in 170 hospitals on one single day, resulting in 1658 patients of whom 1524 were discharged alive. Clinical characteristics including LVEF as well as biological variables (creatininemia, hemoglobin, natriuretic peptides) and treatments were recorded during hospitalization. Changes in treatment between admission and discharge as well as during the 3 ± 1 months following discharge was studied. Changes after discharge were recorded by participating hospitals on a voluntary basis, and by calling referring physicians as well as patients. For the present study, only patients with LVEF ≤ 40% were analyzed. Figures for one-year total mortality after discharge were obtained from the national registry of death (Inserm CepiDC). All patients gave informed consent at the time of inclusion.

Statistical analysis

Continuous variables were expressed as mean ± SD or median (1st and 3rd quartiles) and categorical variables were expressed as frequency and/or percentages. Differences between groups were assessed by 1-way ANOVA with a post hoc Bonferroni's test for multiple comparisons. Categorical variables were compared by using the chi-squared test. Variables associated with prescription of ACE-I/ARB and beta-blockers were studied using logistic regression with all baseline characteristics. Then a stepwise multivariate logistic regression (rearward exclusion iterations) using significant predictors from the univariate analysis ($p<0.20$) was performed. A stepwise cox analysis was performed with the parameters influencing survival. Kaplan Meier survival curves were drawn depending on the prescription of the HF treatment with target dose ≥ 50%. Hazard ratios (HRs) with a 95% CI are given as association measures. All tests were two-sided using a significance level of 0.05. Analyses were performed using MedCalc software.

Results

Among the 1522 survivors at discharge in the OFICA study, a specific follow-up of prescribed medications after discharge was performed by 59 of the 170 participating hospitals resulting in a cohort of 592 patients. Among these 592 patients, only 519 patients of whom 275 had LVEF ≤ 40%, had at least one consultation during the 3 months after discharge and the data was analyzed. The main clinical characteristics as well as discharge clinical and biological variables and treatments are reported in Table 1 and compared to surviving patients at discharge with LVEF ≤ 40% of the whole OFICA cohort (n=733). There was no significant difference between the two groups among all studied variables (Table 1).

The usage of classes of cardiovascular agents on admission, at discharge and at 3 months is detailed in Table 2. The usage of ACE-I or ARB as well as beta-blockers or loop diuretics increased by 20 to 30% when the usage of MRA increased by only 8.4% from admission to discharge. Among beta-blockers on admission, there were only 39.2% beta-blockers that are recommended by guidelines. The rate of antithrombotic agents as well as amiodarone also increased during hospitalization. In contrast, there was no significant change between the time of discharge and 3 months after discharge in the mean rate of prescriptions or dosing of evidence based-HF drugs. The Figure 1 detailed further changes in prescription of loop diuretics, ACE-I or ARB and beta-blockers. Indeed, there was no change in use or dosage of ACE-I or ARB and beta-blockers in most patients after discharge. For

	OFICA cohort LVEF ≤ 40% n=733	Study subgroup LVEF ≤ 40% n=275
Age (years)	76.1 (63.3-83.1)	75.1 (64.5-82.2)
Gender (male)	67%	66%
Previous hospitalization for AHF	46%	42%
Ischemic heart disease	45%	44%
COPD	19%	22%
Hypertension	53%	53%
Diabetes	34%	26%
BMI (kg/m²)	26.2 (23.0-30.2)	25.8 (22.5-30.9)
LVEF	30.0 (22.0-35.5)	31.5 (25.0-40.0)
Sinus rythm	57%	60%
Systolic BP (mmHg)	110 (99-127)	110 (100-130)
Heart rate (bpm)	74 (65-84)	70 (64-80)
Hemoglobin (g/dL)	12.0 (10.7-13.6)	12.3 (11.0-13.5)
Creatininemia (mg/l)	13.0 (10.2-17.4)	12.5 (10.2-17.0)
Kaliemia (mmole/L)	4.3 (3.9-4.6)	4.3 (4.0-4.6)
Worsening renal function*	47%	47%
Discharge DFG <30 ml/min/1.72 m²	19%	19%
BNP (pg/ml)	627 (327-1471)	481 (271-1175)
NT proBNP (pg/ml)	3528 (1346-8482)	2517 (1310-6482)
Loop diuretics	88.6%	88%
ACE-I or ARB	77.7%	79.6%
Beta-blockers	67.4%	69.8%
ACE (or ARB) and beta-blockers	57.9%	59.6%
Mineraloreceptor antagonists	26.6%	23.3%

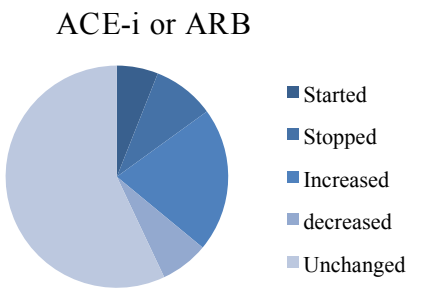
This table shows clinical and biological variables at discharge as well as treatment.

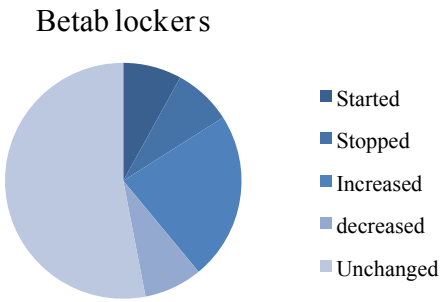
* worsening renal function was defined by increase in creatininemia ≥ 0.3 mg/L between admission and discharge.

Table 1: Baseline characteristics of patients with LVEF <40% from the whole OFICA study and in the subgroup of 275 patients with analysis of treatment at 3 months.

	Admission	At discharge	At 3 months
ACE-I	46.5%	66.2%	64.9%
At ≥ 50% of target dose	65%	42%	42%
at 100% of target dose	34%	13%	14%
ARB	16.3%	13.8%	12.4%
At ≥ 50% of target dose	48%	9%	8%
at 100% of target dose	14%	5%	4%
ACE-I or ARB	62.8%	79.6%	76.3%
At ≥ 50% of target dose	60%	51%	48%
at 100% of target dose	27%	19%	19%
Beta-blocker	39.2%	69.8%	69.0%
At ≥ 50% of target dose	41%	20%	31%
at 100% of target dose	14%	16%	10%
ACE-I or ARB and Beta-blockers	40.1%	59.6%	54.7%
Loop diuretics	68.7%	88.4%	89.1%
dose (mg of furosemide/d)	107 ± 157	93 ± 140	94 ± 152
Mineraloreceptor antagonists	14.9%	23.3%	24.8%
Digitalis	10.3%	9.1%	8.7%
Calcium blockers	12.2%	10.9%	10.1%
Amiodarone	16.3%	20.7%	21.5%
Statins	39.0%	47.9%	47.9%
Aspirin	36.7%	33.5%	33.1%
Anticoagulant	29.3%	41.8%	43.2%
Number of drugs	NA	8 (6-10)	8 (6-10)

Table 2: Comparison of rates of prescription at hospital discharge and at 3 months.





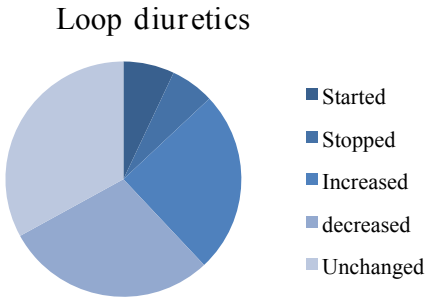


Figure 1: changes in rate of prescription as well as dose between discharge and 3 months.

ACE-I and beta-blockers respectively, increase in dosage after discharge was observed in 21 and 23% of patients. Decrease in dosage after discharge was observed in similar rates. There were few introductions or cessations of these treatments -6 to -9% after discharge. Dosage of loop diuretics was increased in 25% and decreased in 26% of patients. In addition, mineraloreceptor antagonists were started in 7% and stopped in 5% of patients after discharge.

Table 3 shows variables that were associated with usage of ACE-I or ARB and beta-blockers at discharge as well as at 3 months. By using multivariate logistic regression, the usage of ACE-I or ARB at discharge ≥ 50% of target dose was significantly related to admission creatininemia (OR 0.95, 95% CI 0.90-0.99, p<0.03), ACE-I or ARB treatment at admission (OR 0.5162, 95% CI 0, 29-0.91, p<0.0242) and ejection fraction (OR 0.96 CI 95% 0.94-0.97, p<0.03). At 3 months after discharge, the usage of ACE-I or ARB ≥ 50% of target dose were significantly related to usage of ACE-I or ARB at discharge (OR 5.67, 95% CI 3.06-10.51, p<0.0001), age (OR 0.97, 95% CI 0.95-0.99, p<0.015) and the creatininemia at discharge (OR 1.0263, 95% CI 0.99-1.06, p<0.18). The usage of beta-blockers ≥ 50% of target dose at discharge was significantly associated with usage of beta-blockers at admission (OR 1.00, 95% CI 0.99-1.00, p<0.372), COPD (OR 1.68, 95% CI 0.70-4.03, p<0.24), and ischemic heart disease (OR 1.5116, 95% CI 0.67-3.40, p<0.37); at 3 months after discharge, the usage of beta-blockers ≥ 50% of target dose was significantly related to usage of beta-blockers at discharge (OR 4.22, 95% CI 2.20-8.08, p<0.0001) and COPD (OR 0.37, 95% CI 0.18-0.75, p<0.0018). Among the 275 patients who had survived at 3 months, all-cause mortality was 7.6% over the following 9 months. Mortality was related to age, HF duration, COPD, left ventricular ejection fraction, discharge heart rate, creatininemia and ACE-I or ARB and beta-blockers ≥ 50% of target dose. There was no significant difference in mortality related to the prescription or not of ACE-I or ARB and beta-blockers ≥ 50% of target dose at 3 months after discharge after adjustment on age, systolic blood pressure, creatininemia and LVEF (HR=5.2999; 95% IC 1.7369 to 16.1722; p=0.0635). But a clear tendency to deusage mortality. Figure 2 shows survival curves depending on the usage or not of HF treatments at 3 months ACE-I or ARB and beta-blockers ≥ 50% of target dose.

Discussion

This study has two main findings. Firstly, treatment at discharge was far from optimal Secondly, there was no increase in usage or dosage of evidence-based HF drugs during the first months after discharge, even though treatment at discharge was far from optimal. Our study shows that 40% of patients did not receive the combination ACE-I (or ARB) and beta-blockers and 75% did not receive MRA 3 months after in our cohort. The use of MRA was particularly weak if we consider that the usual contra-indications. Insufficient adherence to guidelines has been pointed out for years, and numerous explanations have been given to explain the gap between real life and the guidelines [9-17] even if there has been improvement over time [18]. The ESC HF Long Term survey that was conducted from 2010 reported results close to ours for the usage of ACE-I/ARB and beta-blockers [9].

The post-discharge period has been called the 'vulnerable phase' of HF because of the very high risk of unplanned readmission or death [19]. Therefore optimization of treatment before and early after discharge is clearly mandatory. Our results show medical inertia in the management of HF patients early after discharge. Inertia has been widely discussed in the context of hypertension or diabetes leading to a campaign of sensitization among practitioners [20-22]. In the area of HF, inertia between discharge

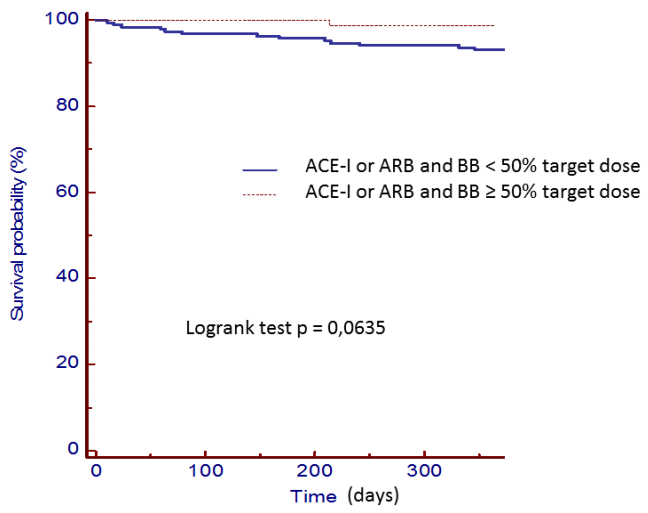


Figure 2: Kaplan meyer survival curves according to treatment with or without ACE-I or ARB and beta-blockers ≥ 50% of the target dose at 3 months.

ACE-I or ARB ≥ 50% of target dose discharge	OR	CI	p	OR	CI	p
Age	0,9871	0,9701 to 1,0043	0,1447			
Gender	0,8189	0,4869 to 1,3774	0,4514			
Discharge creatininemia	0,9564	0,9144 to 1,0002	0,0510	0,9372	0,8955 to 0,9806	0,0050
Hypertension	0,7630	0,4676 to 1,2449	0,2788			
Diabetes	1,5305	0,8772 to 2,6706	0,1340			
Ischemic heart disease	1,5601	0,9550 to 2,5485	0,0757			
Treatment on admission	0,5526	0,3201 to 0,9540	0,0333	0 ,5162	0,2905 to 0,9173	0,0242
Admission systolic blood pressure	1,0037	0,9910 to 1,0165	0,5698			
Ejection fraction	0,9681	0,9429 to 0,9939	0,0156	0,9657	0,9383 to 0,9938	0,0311
ACE-I or ARB ≥ 50% of target dose at 3 months						
Age	0,9773	0,9595 to 0,9955	0,0146	0,9730	0,9517 to 0,9947	0,0152
Gender	0,5474	0,3274 to 0,9154	0,0216			
Discharge creatininemia	0,9945	0,9631 to 1,0270	0,1379	1,0263	0,9879 to 1,0662	0,1823
Hypertension	1,0769	0,6628 to 1,7499	0,7648			
Diabetes	1,2531	0,7124 to 2,2041	0,4336			
Ischemic heart disease	1,1772	0,7223 to 1,9185	0,5126			
Treatment at discharge	1,5222	0,9262 to 2,5016	0,0974	5,6730	3,0614 to 10,5127	<0,0001
Discharge systolic blood pressure	1,0038	0,9911 to 1,0167	0,5620			
Ejection fraction	0,9728	0,9475 to 0,9988	0,0402			

Betablockers ≥ 50% of target dose at discharge	OR	CI	p	OR	CI	p
Age	0,9970	0,9766 to 1,0180	0,7801			
Gender	0,8476	0,4484 to 1,6020	0,6106			
COPD	0,7232	0,3400 to 1,5382	0,0039	1,6848	0,7035 to 4,0347	0,2417
Diabetes	1,5757	0,8264 to 3,0044	0,1673			
Ischemic heart disease	1,2380	0,6859 to 2,2344	0,0478	1,5116	0,6717 to 3,4016	0,3181
Ejection fraction	0,9991	0,9689 to 1,0303	0,9547			
Treatment on admission	2,6149	1,3965 to 4,8962	0,0027	1,0023	0,9973 to 1,0073	0,3704
Discharge heart rate	0,9726	0,9487 to 0,9972	0,0291			
Discharge systolic blood pressure	1,0064	0,9913 to 1,0217	0,4107			
Betablockers ≥ 50% of target dose at 3 months						
Age	0,9929	0,9759 to 1,0102	0,4178			
Gender	0,7650	0,4551 to 1,2858	0,3120			
COPD	0,3391	0,1756 to 0,6550	0,0013	0,3710	0,1840 to 0,7480	0,0018
Diabetes	0,8845	0,5041 to 1,5520	0,6687			
Ischemic heart disease	0,9287	0,5699 to 1,5132	0,7663			
Ejection fraction	0,9736	0,9485 to 0,9993	0, 4383			
Treatment on admission	0,1586	0,0820 to 0,3065	<0,0001	4,2203	2,2016 to 8,0898	<0.0001
Discharge heart rate	0,9968	0,9797 to 1,0141	0,7122			
Discharge systolic blood pressure	1,0052	0,9926 to 1,0179	0,4228			

Table 3: Relationships between prescription of HF treatments at discharge and clinical characteristics. Continuous variables were analysed by ANOVA and categorical variables by Chi2 test. Variables associated with p ≤ 0.20 were tested in multivariate logistic regression. Admission or discharge treatment corresponds to analysed treatment in each row.

and early follow-up has been discussed very little. By comparing medications during an index consultation with discharge (about 6 months before index consultation), authors reported poor changes in the rates of main HF medications in patients with reduced LVEF [23]. By using a large national health insurance database, very few changes in the use of evidence-based HF medications between the period before hospitalization and 30 days later were reported [24]. Our results further refine these points. Our study shows that improvement in medical treatment is made during the hospitalization but not after discharge. We looked for characteristics that could explain the use of HF treatment as well as changes in treatment. As expected, previous use of evidence-based HF medications was by far the strongest predictor of their later usage either at discharge or 3 months after discharge that was also found in the get with the Guidelines–Heart Failure registry [25]. Besides and also unsurprisingly, age was related negatively to the use of HF medications, and COPD was linked to the lack of prescription of beta-blockers at discharge. With MRA, the usage rate in our survey is clearly insufficient, even if we take into account the guidelines applied at the time of inclusion, and the usual contra-indications -severe renal dysfunction and kaliemia ≥ 5.0 mM- were observed in less than 20% and 10% respectively. An explanation for the lower usage of MRA in our cohort is that our survey is more representative of real life, with many hospitals participating.

In many cases, the absence of initiating therapy or an increase of dosage is likely out of concern for possible intolerance. In ambulatory practice, practitioners may prefer to stop increasing the dose of a drug before intolerance occurs, because some adverse events (bradycardia and/or hypotension) are less easily manageable outside hospital. Secondly, the concept of the 'futility' of increasing the dose of a drug shows that the strategy of increasing the dosage to the maximum tolerated level, regardless of the patient's well-being, has not been fully integrated or accepted. Many strategies have been recommended in order to improve the management of HF patients after discharge. For example, an early post-discharge visit is strongly recommended in the current guidelines (5) and it has been reported that there is a strong relationship between the delay of this post-discharge consultation and the outcome [26]. In our study, the delay between discharge and the first outpatient visit was not recorded, but it must be pointed out that 12% of our patients had no consultation during the 3 months following discharge. Other transitional care service strategies, including follow-up phone calls, visiting nurses, telemonitoring, and home weight monitoring have shown some usefulness [27]. Therefore it should be possible to achieve target doses of key medications and improve symptoms without adversely affecting side effect symptoms, electrolytes or renal function.

The death rate in HF patients is much higher after discharge than in chronic HF patients without hospitalization [28]. By using the large OPTIMIZE-HF cohort, authors alearly remove clearly that the initiation of beta-blockers during hospitalization as well as its continuation at discharge was protective against the risk of subsequent events during the one-year post discharge, irrespective of others clinical variables [29,30]. In our study, we show that the use of ACE-I/ARB and beta-blockers rate >50% of the target dose at 3 months remains protective against the risk of death for the next 9 months. Again, this demonstrates the need to treat all eligible patients.

Limitations

The first limitation was our inability to obtain the prescriptions for all patients during the 3 months after discharge. This follow-up was only accepted by 35% of the participating hospitals. There was no significant difference in clinical characteristics or discharge treatment compared to the whole cohort, and the relatively small number of patient and of death weakens our Cox analysis of the prognostic impact of treatment. Secondly, the OFICA was not designed to obtain medical justifications for the lack of prescription of HF-related drugs. Whilst the reasons justifying the prescription of HF-related drugs would appear to be useful data, the acquisition of comprehensive, reliable data is relatively modest for a large multi-centric survey. Therefore our results have to be interpreted cautiously. Thirdly, there was a relatively long interval between the OFICA survey and this analysis. Since the inclusion of patients in the OFICA survey, new guidelines have been published, including new drugs such as ivabradine or Angiotensin Receptors Neprylisin inhibitors, and it can be speculated that practitioners have been further educated and, for example, prescribe MRA more frequently.

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