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Early and short-term intensive management after discharge for patients hospitalized with acute heart failure, a randomized study (ECAD-HF)

Short title: Intensive versus standard early management after acute heart failure

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Abstract

Aims

Hospitalization for acute heart failure (HF) is followed by a vulnerable time with increased risk of readmission or death, thus requiring particular attention after discharge. In this study we examined the impact of intensive, early follow-up among patients at high readmission risk at discharge after treatment for acute HF.

Methods and Results

Hospitalized acute HF patients were included with at least one of the following: previous acute HF < 6 months, systolic blood pressure \leq 110mmHg, creatininemia \geq 180 μ mol/L, or BNP \geq 350 pg/mL or NTproBNP \geq 2200 pg/mL. Patients were randomized to either optimized care and education with serial consultations with HF specialist and dietician during the first 2-3 weeks, or to standard post-discharge care according to guidelines. Primary end-point was all-cause death or first unplanned hospitalization during 6-month follow-up. Among 482 randomized patients (median age 77 and median left ventricular ejection fraction 35%), 224 were hospitalized or died. In the intensive group, loop diuretics (46%), betablockers (49%), ACE-inhibitors or angiotensin receptors blockers (39%) and mineralocorticoid receptor antagonists (47%) were titrated. No difference was observed between the two groups for primary end-point (HR 0.97; 95CI 0.74-1.26), nor for mortality at 6 or 12 months or unplanned HF rehospitalization. Additionally, no difference between the two groups according to age, previous HF and left ventricular ejection fraction was found.

Conclusion

In high-risk HF, we found intensive follow-up early post-discharge did not improve outcomes. This vulnerable post-discharge time requires further studies to clarify useful transitional care services.

Keywords

Heart failure, follow-up, transitional care services, readmission

Introduction

Following hospitalization for acute heart failure (HF), the level of rehospitalization or death is greatly elevated during the first few months, reaching 30-50% after 6 months¹⁻³. Little progress has been made in managing acute HF in recent decades, although significant advances have been made in chronic, stable HF management. Critical time points are discharge from hospital and the transition between discharge and ambulatory care. As observed in other chronic diseases, HF management is subject to medical inertia⁴. In recent years, published guidelines have emphasized the need to follow-up these patients within a multidisciplinary program⁵ and hospital staff have been encouraged to apply these guidelines. Indeed, some countries have even introduced financial penalties if excessive numbers of patients are readmitted early⁶. Disease management programs include various measures, such as: a discharge checklist and planning, telephone follow-up, therapeutic education, telemonitoring, home nurse visits, early follow-up and early commencement of rehabilitation before discharge. Though meta-analyses generally suggest an overall benefit^{7, 8}, results of several of these studies, as well as recent randomized studies, are more equivocal^{9, 10}, despite having strict inclusion criteria. In terms of relevance in clinical practice, many multidisciplinary programs are severely constrained by human and/or financial resources.

At hospital discharge, many patients are clinically unstable, as they are discharged with continuing hypervolemia and symptoms¹¹. In-hospital treatment optimization is difficult as the inpatient period is insufficient to evaluate whether therapy additions or changes improve or worsen a patient's clinical status or co-morbid conditions. Also, coordination between inpatient and outpatient care is often poor¹². Thus, early review post-discharge is necessary and is an opportune time to check clinical and biochemical parameters, rectify any prescription errors, titrate specific HF treatment, reinforce therapeutic education and instigate multidisciplinary tools that had not been established prior to discharge, such as rehabilitation to effort. The ESC/HFA recommendations advise patients be reviewed at 1 week by their general practitioner and, if possible, at 2 weeks by the hospital cardiology team. The efficacy of immediate follow-up has been suggested by observational studies but not been shown by randomized clinical trials¹³⁻¹⁶.

In this study, we aimed to specifically analyze the clinical impact of immediate follow up after hospital discharge for patients treated for acute HF and at high readmission risk. A

sufficiently simple format that was compatible with practice was chosen, in the form of two consultations with a HF specialist cardiologist and a dietetic education consultation in the first two weeks after hospital discharge.

Methods

The Early Care After Discharge of Heart Failure patients (ECAD-HF, NCT01820780) was a randomized, multicentre, open-label study to investigate the effectiveness of serial consultations or standard care to prevent hospitalization or death in patients discharged after an acute heart failure event. The protocol and amendments were approved by the French institutional review board ('Comité de Protection des Personnes'). The study was conducted according to French laws, Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Study participants

The study population consisted of adults ≥ 18 years of age, who were eligible for treatment through the French social security system, who were hospitalized for acute HF. Patients were eligible when they met at least one of the four following criteria at discharge or one day prior to discharge: previous HF hospitalization during the 6 months before inclusion, blood levels of B-type natriuretic peptides (BNP) ≥ 350 pg/ml or NTproBNP ≥ 2200 pg/ml and/or serum creatinine ≥ 180 $\mu\text{mol/L}$ and/or systolic blood pressure ≤ 110 mmHg. Patients were excluded if they had acute coronary syndrome, acute myocarditis, isolated right HF related to pulmonary disease, reversible cause of HF such as tachycardiomyopathy, planned cardiac surgery within a few weeks following discharge, enrolment in another clinical trial, pregnant or breastfeeding, and patients under guardianship or wardship. Patients were also excluded if they had a planned disease management program during the first month after discharge, except if enrolled in the home health assistance program, PRADO, a French national health program that involves weekly nurse visits from discharge to 2 months, in addition to usual care.

Study procedures

The enrolment visit was performed either on or one day before discharge. Patients were randomly assigned (1:1), in a centralized manner, to either intensive or standard care. In standard care, all patients were discharged with a medical report as were prescribed blood tests including plasma electrolytes, natriuretic peptides and a renal function panel. All

patients were encouraged to perform their blood test and obtain their first follow-up appointment with their general practitioner within the first week after discharge and visit their referring cardiologist within the first month. Investigators were also encouraged to have these appointments scheduled by their staff.

Intensive care comprised of planned in-person consultations with a HF specialist (investigators in each centre) and a dietitian at day 7 and day 14 after discharge, in addition to conventional follow-up with a general practitioner and referring cardiologist. A further consultation was encouraged at day 21. Before each consultation, at least plasma electrolytes, natriuretic peptide levels and a renal function panel was obtained. During each consultation, the patient was reviewed to optimize care, including titration of their HF drugs.

Study outcomes

The primary outcome was the composite of all-cause deaths or unplanned hospitalizations at 6 months. The secondary outcomes were: all-cause deaths, unplanned hospitalizations or unplanned hospitalizations for HF at 6 and 12 months. Also, evidence-based HF treatment at 6 months, changes in natriuretic peptide BNP or NTproBNP levels between discharge and the second consultation in the intensive group, natriuretic peptide levels between discharge and 6 months in both groups and the cumulative number of days alive and hospitalization-free days at 6 and 12 months. The following sub-group analyses were planned: left ventricular ejection fraction (LVEF) $<$ or \geq 40%; age $<$ or \geq 75 years; previous history of HF or not. Adverse event data was collected during follow-up consultations with investigators or technicians contacted either patients, family or referring doctors by telephone.

Study management

Patient follow-up, monitoring of study centers and statistical analyses were performed by the clinical research unit at the University Hospital Lariboisiere (Paris, France). For each adverse event during follow-up, medical report was collected and blinded. A clinical events committee adjudicated each death and hospital stay, assessed whether or not it was were planned and assigned the relationship with a cardiovascular or HF event.

Statistical analysis

Continuous variables were reported as means with standard deviation (SD) or as medians with interquartile range (Q1-Q3), if appropriate and were compared using

standardized mean differences. Categorical variables were reported as numbers with percentages and were compared using standardized proportion differences.

The primary analysis was based on the intention-to-treat population and the primary efficacy endpoint was the proportion of patients with all-cause death or unplanned hospitalization within 6 months after hospital discharge. The primary efficacy endpoint related to time to an event, was compared between the intensive group and usual group using a survival analysis based on a Cox model with study center as a random effect. An adjusted Cox model was performed including center as a random effect and prior known risk factors as covariates (age, number of hospitalizations in the last 12 months, chronic obstructive pulmonary disease/chronic respiratory failure, stroke, depression, LVEF, systolic blood pressure, hemoglobin, estimated glomerular filtration rate and natriuretic peptide blood levels (BNP >350 or NTproBNP >1500pg/mL). The survival status was described using Kaplan–Meier curves, hazard ratio (HR), and 95% confidence intervals of the adjusted HR.

The time-to-event secondary endpoints were analyzed using the same methods as for the primary endpoint. The secondary binary endpoints were analyzed using the Cochran-Mantel-Haenzel (CMH) test stratified by center, and Breslow-Day test was performed for homogeneity of the odds ratios. For secondary continuous endpoints that are normally distributed, ANCOVA was used and included baseline endpoints and the covariates mentioned above, with the management groups and center as fixed effects. For secondary continuous endpoints that are non-normally distributed, the non-parametric Van Elteren test stratified by center was used, the same covariates were used as for normally-distributed data.

Pre-specified subgroup analyses to evaluate variations in treatment effect were done using Cox regression models, with terms for treatment, subgroup, and interaction of treatment with subgroup. All reported subgroup analyses were pre-specified.

Assuming an estimated frequency of the composite primary criterion of 35% in the control group, with a reduction in the relative risk of 32% with intensive care, it was estimated that a sample of 554 patients, including a loss to follow-up rate of 10%, would have 80% power to detect a difference in the primary outcome, at a significance level of 0.05 for a 2-sided test.

The two-sided significance level was fixed at 5%. All tests were performed using SAS version 9.4 statistical software (SAS Institute Inc., Cary, NC, USA).

Results

Between July 2014 and May 2018, 495 patients were included in 22 study centers and 13 patients were excluded from statistical analysis because of 2 randomization errors, 10 withdrew their consent and 1 died before discharge, leaving 482 patients in the intention-to-treat analysis: 237 in the intensive arm and 245 in the control arm. The median number of patients enrolled in each hospital was 17 (IQR 7-26; min-max 3-99).

Patient characteristics

Table 1 shows patient clinical characteristics at baseline. No difference was observed between the two groups. Most patients were male (73%), with a median age of 76 years (IQR 65-83). LVEF was ≤ 0.40 in 63% of patients and ≤ 0.50 in 76% patients. Among the four inclusion criteria, patients were admitted with: previous unplanned HF admission (<6 months) in 42%, natriuretic peptides blood levels above cut-offs in 65%, serum creatinine ≥ 180 $\mu\text{mol/L}$ in 22% and systolic blood pressure ≤ 110 mmHg in 44% of patients.

Changes in medication

In the intensive group, most patients were reviewed by the HF team during the first 2 weeks after discharge: 88.2% were reviewed by the HF cardiologist at day 7, 85.2% at day 14, 82.3% at both times, and 76.8% by a dietician at day 7 or 14.

Table 2 shows prescribed drugs in patients before admission, at discharge and at 6 months. Rates of HF drug prescription increased significantly between admission and discharge for diuretics, angiotensin converting enzyme inhibitors (ACEi) or betablockers and for mineralocorticoid receptor antagonists (MRA) in the two groups. At discharge, nearly 85% of patients with LVEF $\leq 40\%$ received ACEi or angiotensin receptor blockers (ARB), more than 90% received betablockers, nearly 45% received MRA and more than 95% received loop diuretics with a median daily dose of 80mg [IQR 40-125]. At 6 months, there was little difference in rate and dosing of the main drugs between the two groups of surviving patients. The median dose of ACEi/ARB was two times higher in the intensive group than the control group. Figure 1 shows changes in HF drugs early post-discharge in patients with altered LVEF in the intensive group. Start or up-titration was more frequent than stop or down-titration for both ACEi/ARB (32% versus 16%) and betablockers (29% versus 10%). Prescribed doses also increased slightly: $\geq 50\%$ of maximum doses of ACEi/ARB were reached in 45% of patients at discharge and 49% of patients at day 14, and in 44% and 49% for betablockers. There was no significant change in blood pressure [median change 2.0 mmHg

(IQR -9.0 ; 15.0)] nor in weight 0 kgs (IQR -2.0 ; 2.0), serum creatinine 0 $\mu\text{mol/L}$ (IQR -12.0 ; 20.0) or natriuretic peptide levels [BNP 19.0 pg/mL (IQR -130.0 ; 221), NTproBNP 337.0 (IQR -1092 ; 1895)] between discharge and the second planned consultation in the intensive group.

Outcomes

Figure 2 displays the cumulative occurrence of events over the 6-month follow-up; there was no difference between the two groups. The number of events for the primary outcome during the 6-month study period was 109 (45.6%) in the intensive group and 115 (46.9%) in the control group [hazard ratio (0.97 95CI 0.74; 1.26)]. Cox analyses of primary and main secondary outcomes are detailed in Table 3. The number of first unplanned hospitalizations for HF during the 6-month study period was similar in the two groups: 46 (19.4%) for the intensive group and 49 (20.0%) for the control group. Median numbers of days alive and hospitalization-free at 6 months were 105 (IQR 30 ;183) in the active group and 130 (IQR 36 ;183) in the control group ($p = 0.77$). Figure 3 displays first unplanned hospitalization rates for any cause or death during the 6-month study period according to pre-specified sub-groups: (A) age $<$ and \geq 75years; (B) LVEF \leq or $>$ 40% %; (C) previous or no history of HF. There was no difference between the intensive and control groups regarding these subgroups.

Discussion

This study found little clinical impact of immediate follow up after hospital discharge for patients treated for acute HF at high readmission risk. Specifically, our results suggest that an intensive follow up, during the first two weeks after hospital discharge, is not enough to improve early outcomes for patients at high risk. Importantly, European guidelines⁵ recommend that acute HF patients see their general practitioner within a week and their cardiology team within 2 weeks of hospital discharge. Yet real-world data suggest that this level of follow-up is not achieved in more than 50% of patients¹⁷. As observed in other chronic diseases, HF management is also subject to medical inertia^{4, 18}. Therefore, it would be of value to gather evidence on which to base a prospective active clinical follow-up of HF patients post-hospitalization. Several factors may explain, at least in part, the lack of difference observed in outcomes between intensive follow up and standard care of patients in this study. Firstly, the patient cohort included very high risk, elderly patients with many

comorbidities. Indeed, death or rehospitalization made up nearly 50% of events at 6 months and the median patient age was 77 years. In such a population, it is possible that hypotension, renal failure, and frailty limited the capacity for improvement in medical therapy and the opportunity to improve outcomes in the Intervention group. This is supported by the lack of a difference in between-group provision of medical therapy during follow up.

Secondly, a key element to improve prognosis is the ability to introduce and quickly adjust appropriate doses of evidence-based HF medication^{19, 20}. In our study, most patients with HF with reduced ejection fraction (HF-rEF) were discharged with a prescription for evidence-based HF treatments (>75% for betablockers or ACE-inhibitors or ARB, and 36% for MRA), and thus the margin/opportunity for improvement was limited. A similar limitation might explain the lack of benefit of BNP-guided management reported in the Guide-it trial²¹. Our Kaplan-Meier curves show a more linear increase in events over time than previous studies or surveys. This could be explained by the fact that patients had severe disease but were discharged with a high level of optimization of both decongestion and HF treatment.

Thirdly, immediate medical consultation post-discharge, even with a specialist HF cardiologist and a dietician, was insufficient and lacked in other essential elements such as more prolonged intensive follow-up or in-home follow up by specialist HF nurses. Regarding the latter, it is noted that there was only a small network of HF nurses operating at the time in France, which prevented such integration into the present study. Also, it is worth noting that non-adherence to HF medications is common, and significantly impacts outcomes²².

While we cannot conclude from our study what measures would constitute an effective transitional care service for HF patients, it is still probable that a successful model would likely comprise direct patient follow-up by HF specialist nurses as well as ongoing disease management by other relevant healthcare professionals, as well as therapeutic education, and would require repeated consultations over a prolonged period. Indeed, a Cochrane review⁸ found evidence for a positive effect of disease management clinics and nurse case management for post-hospital HF care. Such a sustained disease management program would require formal collaboration between doctors and the relevant health and educational professionals. However, the clinical benefit of proposed non-medical interventions in the transition period, such as education, telehealth or involvement of pharmacists, is still unproven, even though many deem such elements to be essential in a

multidisciplinary program. For example, telemonitoring only appears beneficial if it is intensive and incorporates a high level of responsiveness to alerts, requiring significant human and logistical resources²³. In the future, telemonitoring may become more feasible with more parameters monitored and being integrated into algorithms known to increase clinical benefit. Early rehabilitation, started during hospitalization, has also recently been shown to be at least of physical benefit, though it does not reduce the rate of readmissions²⁴.

Lastly, it is probable that transitional care services will need to be adapted to specific patient clinical profiles, patient wishes and available resources. While the present study did not reveal specific improvements for post-hospitalization HF care, sound evidence for development of transition program elements is still needed for the design of an effective, albeit costly program. The fact that so many patients deteriorate after hospital release indicates that such further investigations are critically required.

Our study does have some limitations. Although unlikely¹⁷, it is possible that patients in both groups received a similar level of immediate post-hospital care as the intensive group. This possibility was not controlled for because we lack sufficiently precise information regarding the exact nature of the medical follow up in the control group. However, we can assume that early follow up in the control group was likely far from optimal according to a recent survey¹⁷ and national health insurance system data showing that not more than 50% patients see their GP within the first month after discharge and not more 50% patients see their referring cardiologist within the first three months. Because of the lack of evidence-based care for HF patients that had preserved LVEF, it is possible that this group of patients were unable to gain as much benefit from the immediate follow up. However, controlling for LVEF in the data analysis showed no difference between the groups. Angiotensin Receptor Nephilysin inhibitors were available only at the end of the inclusion period; consequently their clinical impact during early therapeutic optimization could not be assessed in this study.

Conclusion

In high-risk HF patients, we found no improvement in outcomes using more intensive follow up in the early period after discharge from hospital when compared to standard care.

This vulnerable post-discharge time, with a high risk of readmission, should be the subject of future studies in order to specify optimal transitional care services.

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Conflict of interest

The authors state that they have no conflict of interest to declare.

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LEGENDS

Table 1: Baseline characteristics and comparison between intensive and control groups.

Quantitative variables are given with median and interquartile range (IQR).

* 'Socially isolated' was defined as the lack of family or relationship/friend during hospitalization

** Worsening renal function was defined as an increase in serum creatinine >26.5% or estimated glomerular filtration rate (eGFR) > 25% at any time during hospitalization.

CRT means cardiac resynchronization therapy with (CRT-D) or without defibrillator (CRT-P).

Table 2: prescribed HF drugs in patients with LVEF \leq 40% at admission, at discharge and at 6 months and comparison between intensive and control groups. Are indicated rates of prescription for each drug; daily doses for loop diuretics and % maximal doses for angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) or betablockers (median and interquartile range (IQR)). MRA means mineraloreceptor antagonist.

Table 3: primary and main secondary outcomes and comparison between the two groups by Cox model.

*Adjustment was done by each centre with random effect and prior known risk factors as covariates: age, number of hospitalizations in the last 12 months, chronic obstructive pulmonary disease/chronic respiratory failure, stroke, LVEF, systolic blood pressure, hemoglobin, effective glomerular filtration rate (eGFR) and natriuretic peptides blood levels (BNP \geq 350 or NTproBNP \geq 1500pg/mL)

Figure 1: Changes in HF drugs in patients with LVEF \leq 40% between discharge and day 14 in the intensive group.

Figure 2: Time to first unplanned hospitalization for any cause or death from any cause during the 6-month study period

Figure 3: Forest plot for pre-specified subgroup analyses of the primary end-point

Table 1

	Active group (n = 237)	Control group (n = 245)
Age (years, median, IQR)	77.3 [IQR 67.9; 84.4]	76.3 [IQR 65.4; 83.4]
Women	27.0%	26.9%
Socially isolated patients*	33.0%	27.8%
Body mass index	25.7 [IQR 22.9;29.1]	25.1 [IQR 22.5;28.7]
Diabetes	37.4%	38.5%
Arterial hypertension	70.0%	71.2%
Chronic obstructive pulmonary disease	18.1%	19.6%
Previous history of HF	73.8%	71.4%
Previous acute HF hospitalization <6 months	41.3%	40.8%
Permanent/paroxysmic atrial fibrillation	38.5/28.7%	42.2/28.3%
LVEF (median, IQR)	0.35 [IQR 0.27;0.47]	0.35 [IQR 0.26;0.47]
LVEF ≤40%	62.9%	63.7%
LVEF ≥50%	23.2%	24.1%
Ischemic cardiopathy	45.2%	40.8%
CRT-P/CRT-D	4.8/11.3%	3.8/8.1%
Main acute HF patterns		
- Pulmonary edema	27.6%	22.3%
- Cardiogenic shock	2.5%	3.7%
Worsening renal function**	27.5%	25.2%
Discharge systolic blood pressure (mmHg)	114 [102;132]	114 [102;129]
% systolic BP ≤ 110mmHg	43.2%	44.0%
Discharge BNP level (pg/mL)	401 [185-743]	584 [273;1220]
% BNP ≥ 350pg/mL	54.2%	69.2%
Discharge NTproBNP level (pg/mL)	3470 [1645;7040]	3267 [1860;6552]
% NTproBNP ≥ 2200 pg/mL	67.4%	67.7%
Discharge eGFR (mL/min/1.73m ²)	41 [31;60]	42 [29;65]
% serum creatinine ≥ 180μmole/L	22.4%	21.7%

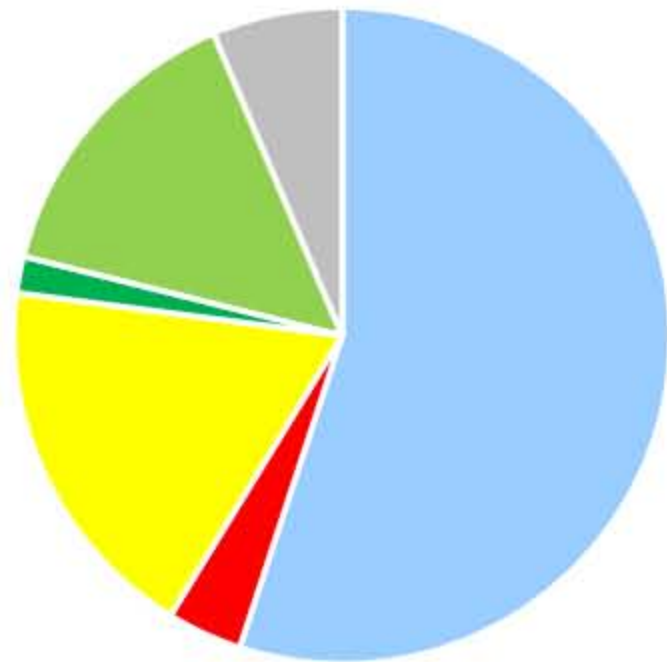
Table 2

	Intensive group LVEF ≤40%			Control group LVEF ≤40%		
	Admission	Discharge	6 month	Admission	Discharge	6 month
Loop diuretics	65.9%	96.2%	89.1%	67.2%	97.0%	91.2%
median dose (mg furoside)	50 [IQR 40;120]	80 [IQR 40;125]	80 [IQR 40;160]	80 [IQR 40;125]	80 [IQR 40;142]	80 [IQR 40;160]
ACE-i or ARB	55.8%	84.6%	78.0%	56.8%	84.1%	74.6%
median dose (% maxi dose)	NA	25 [IQR 17 ;33]	33 [IQR 17 ;50]	NA	17 [IQR 17 ;33]	17 [IQR 17 ;33]
Betablockers	61.7%	93.1%	93.3%	62.6%	93.9%	93.3%
median dose (% maxi dose)	NA	38 [IQR 25;50]	38 [IQR 25;75]	NA	38 [IQR 25;75]	50 [IQR 25;75]
MRA	19.4%	40.6%	34.4%	19.7%	48.1%	41.7%
Digoxin	2.3%	2.3%	1.1%	1.5%	1.5%	1.9%
Ivabradin	0.0%	2.3%	1.1%	1.5%	4.6%	1.0%
Calcium blockers	23.1%	16.0%	12.5%	12.2%	9.8%	11.7%

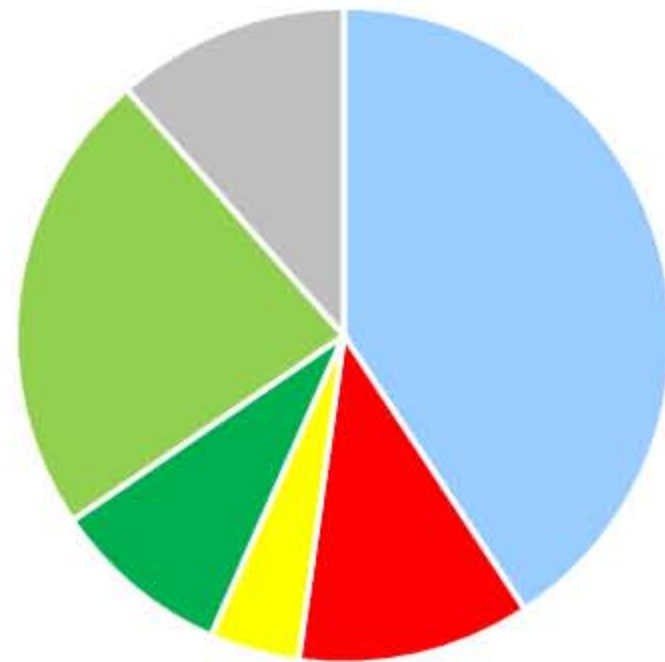
Table 3

	Unadjusted Cox Model				Adjusted Cox Model*	
	Intensive group (n=237)	Control group (n=245)	Hazard-ratio (95% CI)	P-value	Hazard-ratio (95% CI)	P-value
All-cause death or unplanned hospitalization at 6-month	45.6%	46.9%	0.97 (0.74;1.26)	0.80	0.99 (0.72;1.37)	0.95
All-cause death at 6- month	12.2%	9.8%	1.27 (0.74;2.19)	0.38	1.29 (0.70;2.36)	0.41
All-cause death at one- year	16.9%	17.6%	0.98 (0.64;1.51)	0.94	1.03 (0.63;1.68)	0.90
Unplanned HF-related hospitalization at 6 months	19.4%	20.0%	0.97 (0.65;1.46)	0.90	1.01 (0.60;1.71)	0.96
All-cause death or unplanned hospitalization at 12-month	57.4%	55.9%	1.05 (0.82 ;1.33)	0.71	1.23 (0.91 ;1.65)	0.18

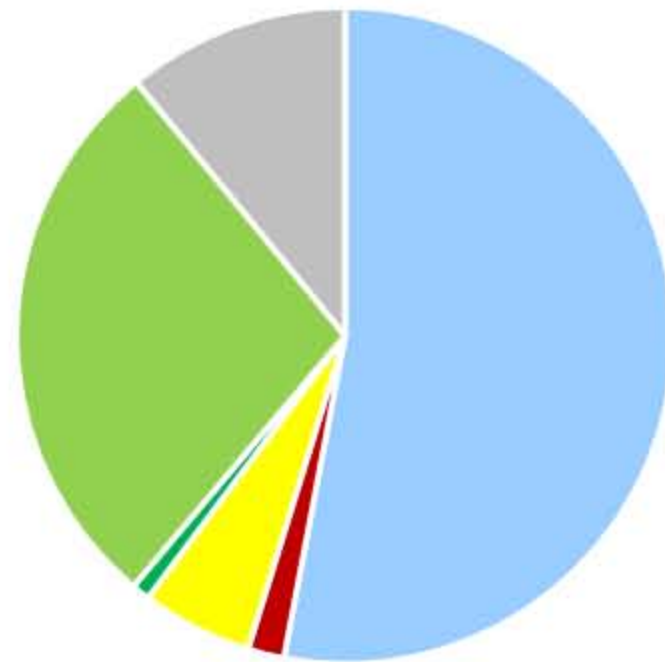
Loop diuretics



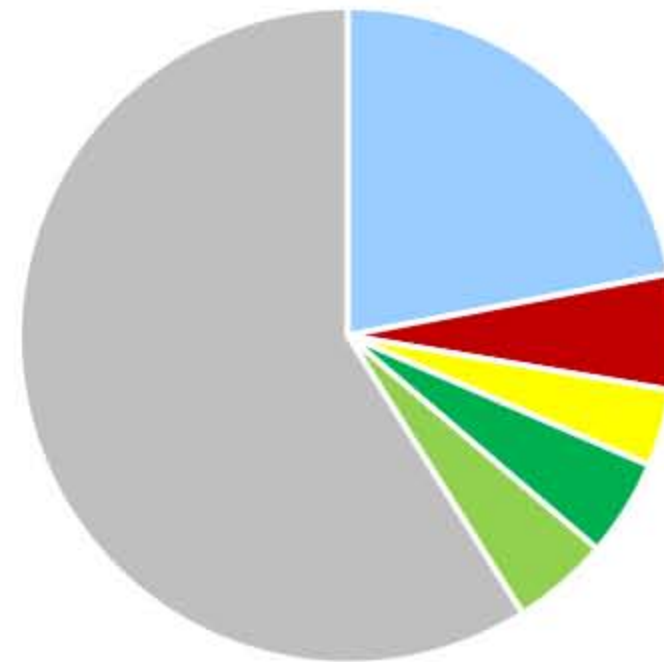
ACEi/ARB



Betablockers



MRA



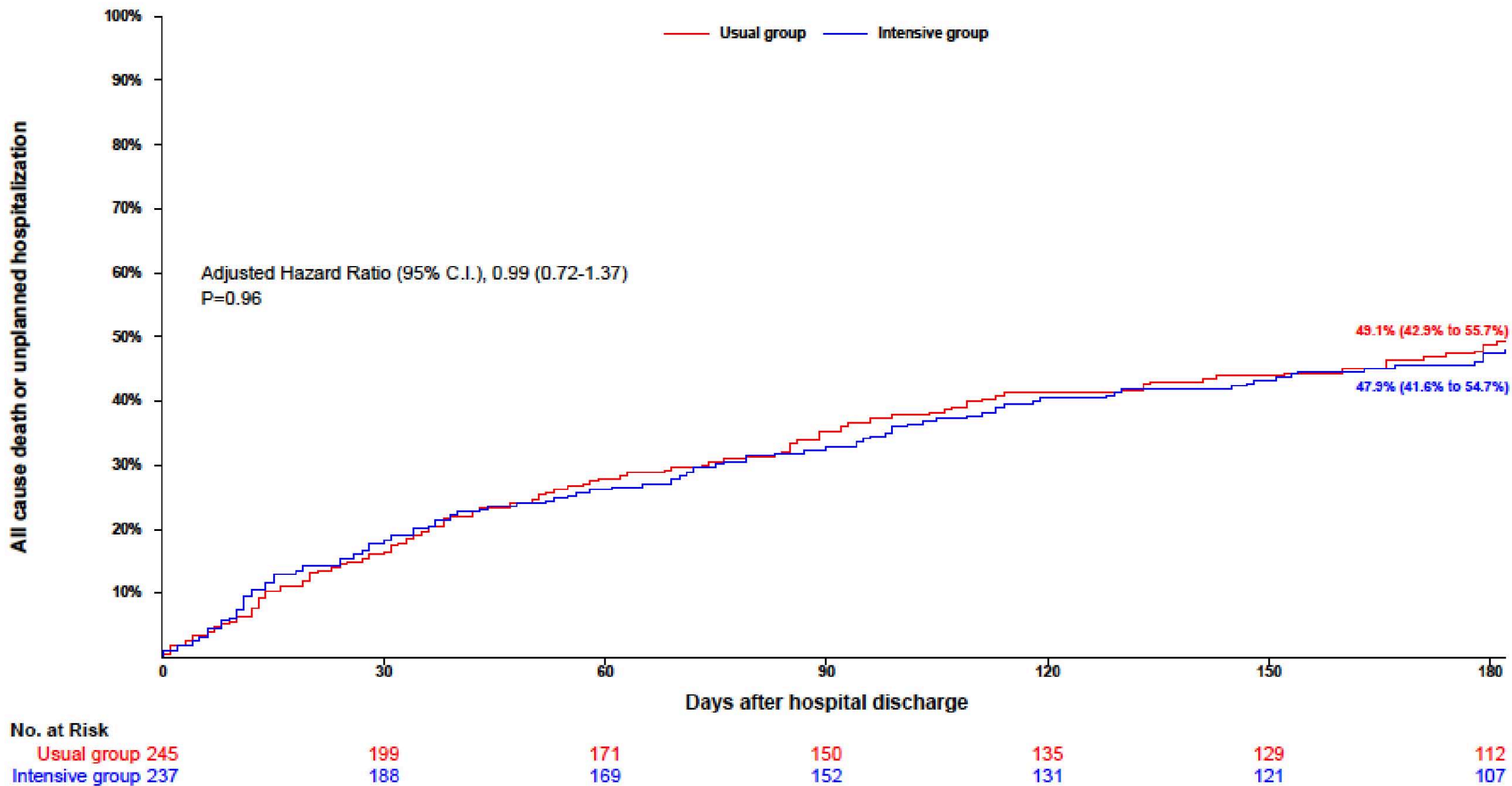
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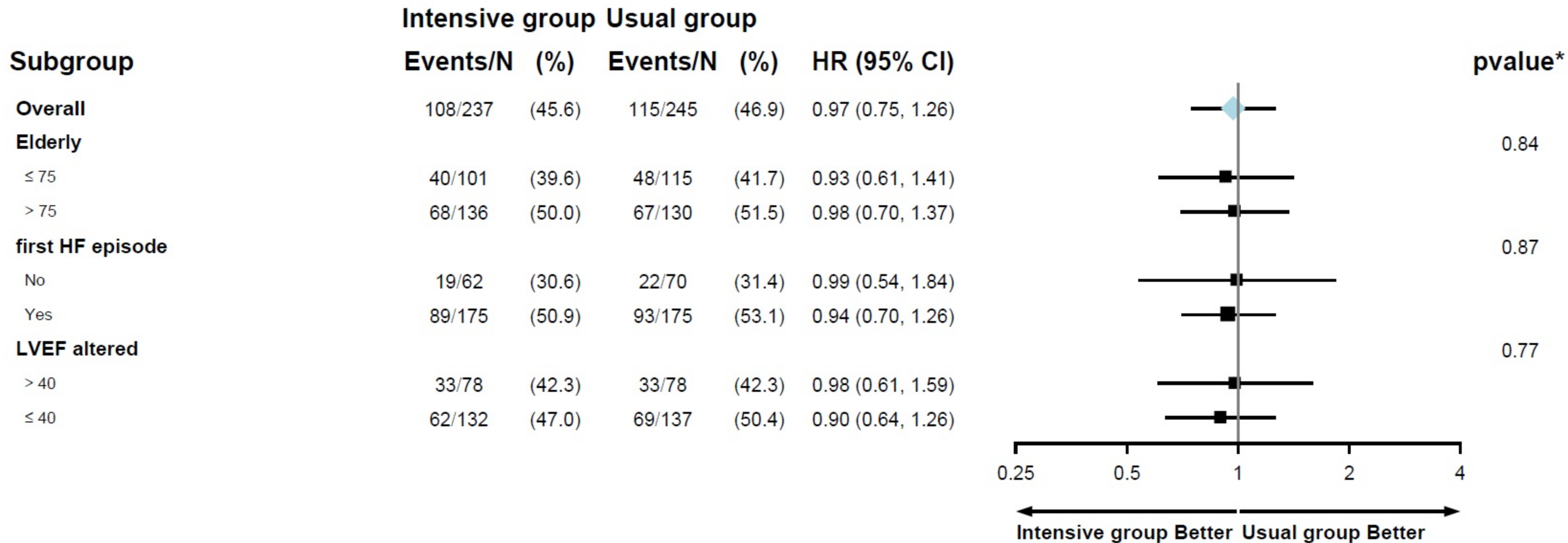
 stop

 decrease

 start

 increase





* The p-value is from the test statistic for testing the interaction between the treatment and any subgroup.