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ORIGINAL RESEARCH

One-Year Mortality After Intensification of Outpatient Diuretic Therapy

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BACKGROUND: Mortality is increased following a hospitalization for decompensated heart failure (HF), during which diuretics are usually intensified. It is unclear how risk is affected after outpatient intensification of diuretic therapy for HF.

METHODS AND RESULTS: From nationwide administrative registers, we identified all Danish patients who were diagnosed with HF from 2001 to 2016 and received angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and β blocker within 120 days. Subsequent follow-up tracked progressive events of diuretic intensification and HF hospitalization. Intensification events were defined as new addition or doubling of loop diuretic or addition of thiazide to loop diuretic. These events were included in multivariable Cox regression models, calculating 1-year mortality hazard after each year since inclusion. Patients with an intensification event or hospitalization were risk set matched to 2 nonworsened HF controls and absolute 1-year mortality risks were calculated using Kaplan-Meier estimates. We included 74 990 patients, their median age was 71 years, and 36% were women. Intensification events were associated with significantly increased mortality at all times during follow-up. One-year mortality was 18.0% after an intensification event, 22.6% after HF hospitalization, and 10.4% for matched controls with neither. In a multivariable Cox model adjusted for age, sex, ischemic heart disease, atrial fibrillation, chronic obstructive pulmonary disease, and diabetes mellitus, the hazard ratio for 1-year death after an intensification event was 1.75 (95% CI, 1.66–1.85), and it was 2.28 (95% CI, 2.16–2.41) after HF hospitalization.

CONCLUSIONS: In a nationwide cohort of patients with HF, outpatient intensification events were associated with almost 2-fold risk of mortality during the next year. Although HF hospitalization was associated with a higher risk, the need to intensify diuretics in the outpatient setting is a signal to review and intensify efforts to improve HF outcomes.

Key Words: diuretics ■ heart failure ■ hospitalization ■ mortality ■ outpatient

See Editorial by Khan et al.

Hospitalizations for decompensated heart failure (HF) are associated with increased mortality risk after discharge.[1,2] As one of the main interventions during HF hospitalization is intensification of diuretic therapy, this intervention may confer increased risk even in the absence of hospitalization, as recently demonstrated in the PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ACEI [Angiotensin-Converting Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial setting,[3,4] in which patients were followed up, examined, and evaluated per protocol by investigators supported in a clinical trial environment. In everyday practice, patients with HF are characterized by higher age and burden of comorbidities, and decisions about diuretic therapy may have different implications for prognosis.

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CLINICAL PERSPECTIVE

What Is New?

- Outpatient diuretic intensification events are frequent among patients with heart failure and are associated with a significantly elevated mortality risk.

What Are the Clinical Implications?

- Patients with an outpatient intensification event should receive as careful a reevaluation for optimization of drug therapy and consideration of advanced options as patients who are hospitalized for worsening heart failure.

Nonstandard Abbreviations and Acronyms

ACEI	angiotensin-converting enzyme inhibitor
COPD	chronic obstructive pulmonary disease
DOSE	Diuretic Optimization Strategies Evaluation
HF	heart failure
ICD-10	*International Classification of Diseases, Tenth Revision*
PARADIGM-HF	Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure

Data on how often oral diuretic therapy is intensified without hospitalization are sparse. Higher doses of loop diuretics are associated with increased mortality,[5] but whether this is caused by the dose increase or the clinical instability that triggered the dose increase is not fully understood.[6] Increasing occurrence of treatment for fluid retention without hospitalization may lead to underestimation of the rate of HF progression if only hospitalization is considered a marker of risk. Even with use of guideline-directed medical therapy and patient education, patients may still progress to stage D HF in an outpatient setting.[7] One clue to such progression may be intensification of diuretic therapy, triggered by members of the HF care team, by physicians outside the HF team, or by the patients themselves. To not miss an opportunity to recognize and address development of advanced HF in outpatients, it is crucial to understand how often outpatient intensification of oral diuretic therapy occurs in clinical practice and the prognostic implications of these intensification events.

Consequently, the aim of this study was to determine the frequency and subsequent mortality for patients after an outpatient intensification event compared with HF hospitalization.

METHODS

The study was a retrospective cohort study based on nationwide Danish administrative registers. The data were provided by Statistics Denmark, and cannot be made available alongside the article. All patients with incident HF were identified using *International Classification of Diseases, Tenth Revision* (*ICD-10*; coded I50 [HF] and I42 [cardiomyopathy]), in the National Patient Register, which holds information on all hospital contacts, inpatient and outpatient, since 1978.[8,9] As we focused on the trajectory for patients who were initially stabilized onto recommended therapies, we enrolled those who were alive at 4 months after diagnosis, had not had a HF hospitalization since diagnosis, and were treated with ACEI/angiotensin receptor blocker and β-blocker therapy. If a patient had a new HF hospitalization during the initial 4 months, the patient would have inclusion postponed for an additional 4 months. Information on medical use was obtained from the National Register of Medicinal Products Statistics, where all collected prescriptions have been registered since 1995. This medical inclusion criterion increased the likelihood of HF with reduced ejection fraction, as data on left ventricular ejection fraction were not available. Information on birth, migration, and death was obtained from the Central Person Register. The Danish Civil Registration System enabled us to identify a person in several registers, so the only patients lost to follow-up were those leaving the country. The patients were followed up for 5 years or until the end of 2017, death, or migration, whichever came first.

Baseline medical therapy was defined as minimum one claimed prescription within 180 days before inclusion. Baseline comorbidity was defined as inpatient or outpatient diagnoses within 5 years before inclusion.

Outcomes of interest during follow-up were intensification events (defined below) and overnight hospitalizations with HF as primary diagnosis at discharge. The primary end point was all-cause mortality.

Intensification Events

Intensification events were defined as newly prescribed peroral loop diuretics of minimum 80 mg/d furosemide equivalent **or** doubled dosage of furosemide equivalent compared with initial dosage to minimum 160 mg/d **or** newly prescribed thiazide in addition to ≥160 mg/d furosemide. To reduce the risk of underclassification, if a patient was hospitalized with HF within 30 days after an intensification event, the patient was only considered as having a HF hospitalization. Intensification

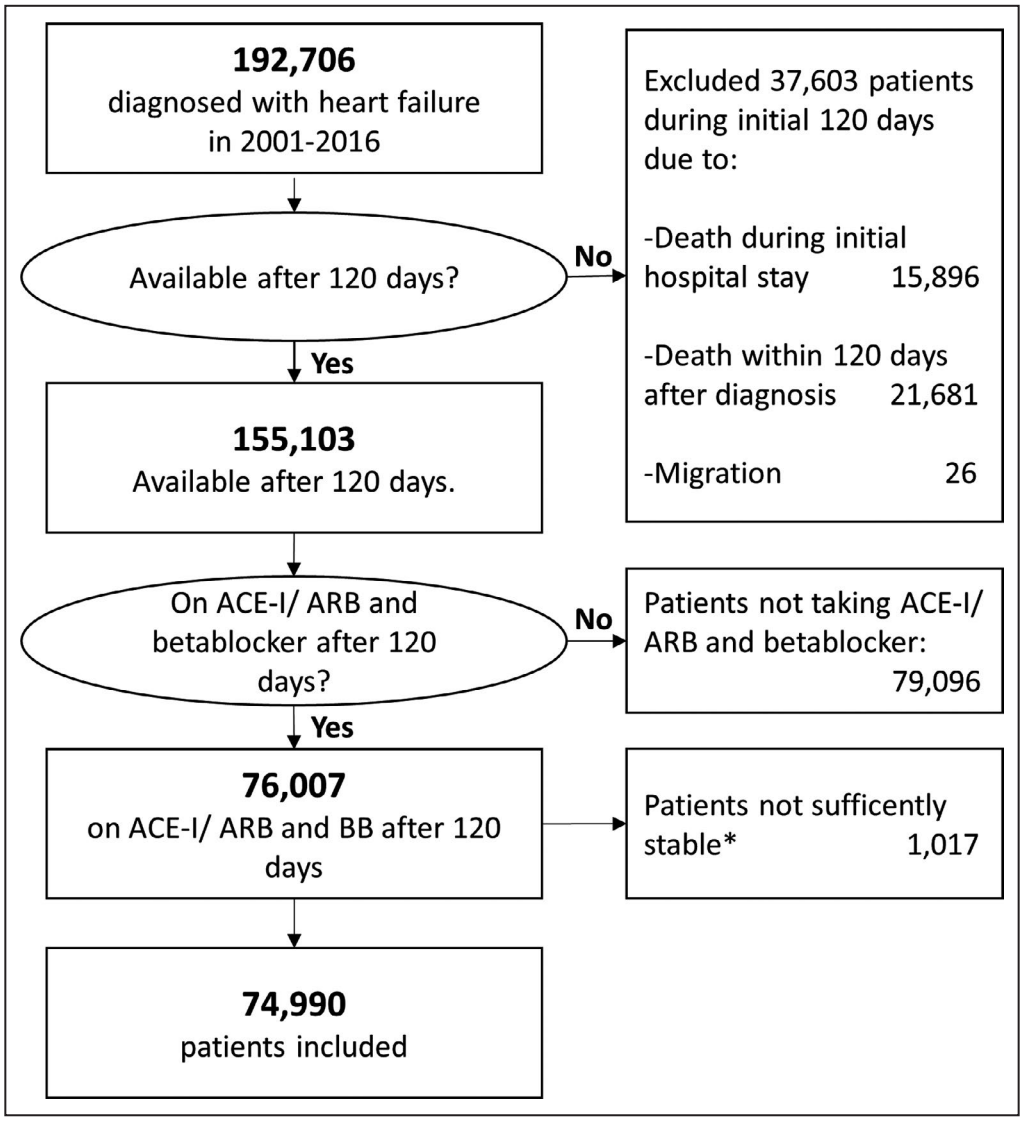

Figure 1. Diagram showing selection of study population.
*Patients who were readmitted within the initial 120 days, followed up for an additional 120 days, and had a second (or third, if diagnosed as inpatient) hospitalization. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and BB, β blocker.

of diuretic therapy during a hospitalization was not adressed, as data on in-hospital treatment were not available.

Statistical Analysis

Baseline characteristics were presented as number and percentage for categorical variables and median and interquartile range for continuous variables. Incidences of intensification events and HF hospitalizations were presented as events per 100 person-years. For the main analysis, we followed up the patients for 5 years after inclusion. After each year period, patients were subdivided into groups on the basis of status: no worsening, intensification event, HF hospitalization, or both types of worsening. Differences in 1-year mortality hazard rates were assessed using multivariable Cox regression models, adjusted for age, sex, diabetes mellitus, chronic obstructive pulmonary disease (COPD), ischemic heart disease, previous myocardial infarction, atrial fibrillation, and stroke. Patients with a worsening event 1 year were not included in the analyses for subsequent years. In this analysis, a person could only contribute to an analysis if the person survived until the end of the given time period, and differences could be underestimated if one worsening event type was associated with a higher mortality hazard immediately after the event than the other. Therefore, in a secondary analysis, we matched each patient with an intensification event or a hospitalization

with 2 controls from the study population, using the risk set matching principle. Absolute risk of 1-year mortality was assessed using the Kaplan-Meier estimator, and differences were assessed with multivariable Cox regression models, adjusted for age, sex, diabetes mellitus, COPD, ischemic heart disease, previous myocardial infarction, atrial fibrillation, and stroke. All Cox regression models fulfilled the proportional hazard assumption. The level of statistical significance was set to 5%. All analyses were conducted in SAS version 9.4 (SAS Institute) and R version 3.5.1.[10]

Ethical Approval

The present study was based on anonymous data from the Danish nationwide administrative registers and, therefore, approval from the local ethics committee was not necessary. The study was approved by the Danish Data Protection Agency (project No. P-2019-262).

RESULTS

Study Population

We identified 192 706 patients with incident HF in the period from 2001 to 2016. After exclusion of 37 603 patients who died at hospital or during the initial 4 months or migrated, exclusion of 79 096 patients who did not receive treatment with ACEI/angiotensin receptor blocker and β blocker, and exclusion of 1017 patients who were considered unstable because of early repetitive hospital admissions, 74 990 patients were included in the study (Figure 1). The median age was 71 years, and 36% were women. Half of the population had a history of ischemic heart disease, and a third had known history of atrial fibrillation (Table).

Worsening Events

Both intensification events and hospitalizations were common early during follow-up, with the highest

Table. Baseline Characteristics for All Included Patients and Stratified on Worsening Status After the First Year Among Patients Still Alive After the First Year (n=62 413)

Characteristic	All Patients (N=74 990)	No Worsening Event (N=53 794)	Intensification Event, Outpatient (N=4517)	HF Hospitalization (N=3160)	Both Events (N=942)
Demographics					
Age, y	71 (62–78)	70 (61–78)	72 (64–80)	70 (60–77)	72 (63–80)
Female sex	27 088 (36)	19 160 (36)	1695 (38)	963 (30)	317 (34)
Nursing home	3906 (5)	2595 (5)	286 (6)	117 (4)	56 (6)
Inpatient primary diagnosis	50 210 (67)	35 153 (65)	2949 (65)	2024 (64)	588 (62)
Comorbidity					
Ischemic heart disease	38 178 (51)	27 529 (51)	2379 (53)	1661 (53)	514 (55)
Previous myocardial infarction	21 459 (29)	15 626 (29)	1229 (27)	878 (28)	240 (25)
Atrial fibrillation	25 336 (34)	17 589 (33)	1493 (33)	970 (31)	336 (36)
Stroke	6888 (9)	4504 (8)	458 (10)	294 (9)	100 (11)
Diabetes mellitus	14 087 (19)	9243 (17)	1070 (24)	673 (21)	247 (26)
COPD	7711 (10)	4850 (9)	546 (12)	313 (10)	109 (12)
Chronic renal disease	2955 (4)	1592 (3)	291 (6)	113 (4)	49 (5)
Malignancy	3319 (4)	3029 (6)	289 (6)	152 (5)	47 (5)
Medical therapy					
MRA	24 217 (32)	16 571 (31)	1418 (31)	1372 (43)	345 (37)
Loop diuretics	53 137 (71)	36 830 (68)	3167 (70)	2541 (80)	676 (72)
Thiazide diuretics	16 472 (22)	11 860 (22)	1165 (26)	625 (20)	259 (27)
Digoxin	17 864 (24)	12 662 (24)	1087 (24)	698 (22)	232 (25)
Aspirin	51 077 (68)	37 135 (69)	3179 (70)	2176 (69)	667 (71)
Statins	44 595 (59)	32 413 (60)	2715 (60)	1976 (63)	573 (61)
Warfarin	22 397 (30)	16 598 (31)	1350 (30)	968 (31)	306 (32)
Nonmedical therapy					
ICD/CRT	4047 (5)	2982 (6)	216 (5)	195 (6)	52 (6)

Data are given as median (interquartile range) or number (percentage). COPD indicates chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; and MRA, mineralocorticoid receptor antagonist.

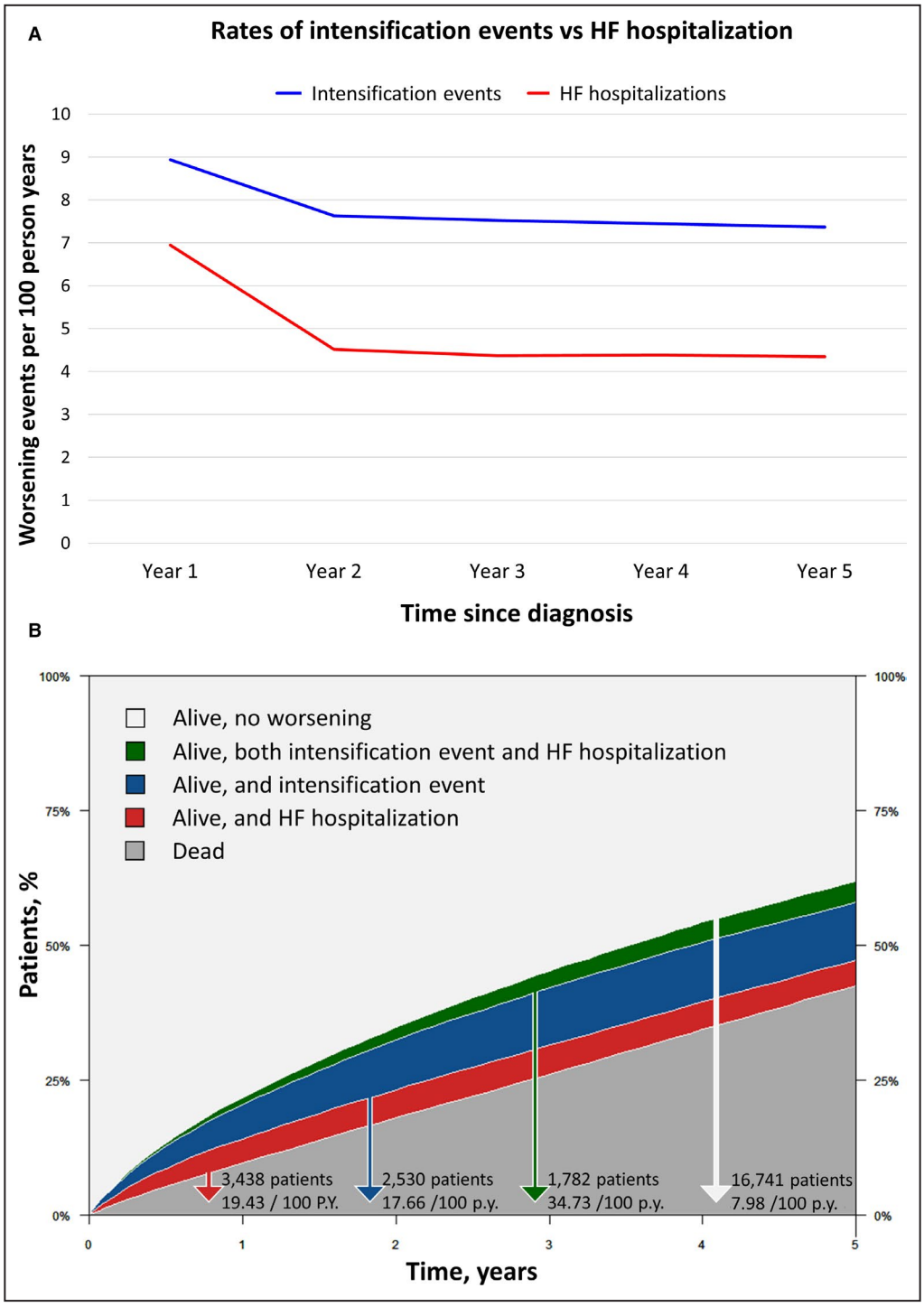

Figure 2. Incidence of worsening, patient status during follow-up, and associated death rates. **A**, Incidences of intensification events and heart failure (HF) hospitalizations according to years since HF diagnosis. **B**, Multistate model showing how many patients are in the 5 possible states at any time during 5 years of follow-up. Arrows indicate how many patients die from each state and death rates per 100 person-years (P.Y.).

incidence rates observed within the first year of follow-up (9 per 100 person-years intensification events and 7 per 100 person-years HF hospitalizations), and more stable, lower incidence rates for the following 4 years (Figure 2A). Only 2% of the hospitalizations were preceded by an intensification event within 30 days. The patient status at any time during follow-up is illustrated in Figure 2B.

Compared with patients with a HF hospitalization within the first year of follow-up, patients with

intensification events were slightly older and were more frequently living in a nursing home. The frequency of mineralocorticoid receptor blocker use was lower in this group. Otherwise, the 2 groups were comparable (Table).

Mortality Risk

Both intensification events and hospitalizations were associated with significantly increased 1-year mortality at all times during follow-up compared with no worsening (Figure 3). During follow-up, the hazard ratio of 1-year mortality for patients with an intensification event ranged from 1.48 to 1.99 compared with patients with no evidence of worsening. During the first 3 years, the hazard ratio of 1-year mortality was significantly higher for patients with a hospitalization compared with patients with an intensification event. Hereafter, no significant differences between mortality after the 2 modes of worsening were observed, although the risk remained numerically higher after a hospitalization. Of the patients who died during follow-up, 57.2% died in hospital, 32.2% died at home, and the rest were not accounted for. In-hospital mortality was slightly higher for patients having a hospitalization (59.0%) than for patients having an outpatient intensification event (55.7%).

In the risk set matched analysis, 2910 patients died after an intensification event, corresponding to an absolute 1-year risk of 18.0% (95% CI, 17.3%–18.7%), compared with 2741 patients after a HF hospitalization, corresponding to an absolute 1-year risk of 22.6% (95% CI, 21.7%–23.5%), and 2437 matched controls, corresponding to an absolute 1-year risk of and 9.8% (95% CI, 9.5%–10.1%). The hazard ratio after the intensification event was 1.75 (95% CI, 1.66–1.85; $P<0.001$), and it was 2.28 (95% CI, 2.16–2.41; $P<0.001$) after the first hospitalization, both compared with matched controls. We observed similar tendencies in all subgroups. For patients initially diagnosed as outpatients, patients aged <70 years, and patients with COPD, there was no significant difference in mortality hazard after intensification events and hospitalizations (Figure 4).

Intensification Events

Having an intensification event was associated with increased risk of HF hospitalization compared with the matched controls, although it was relatively rare, with a cumulative incidence of 8.8% (95% CI, 8.0%–9.6%) after the first year, as illustrated in Figure S1A. Figure S1B illustrates that intensification events were associated with significantly increased risk of HF hospitalization-free mortality, implying that the

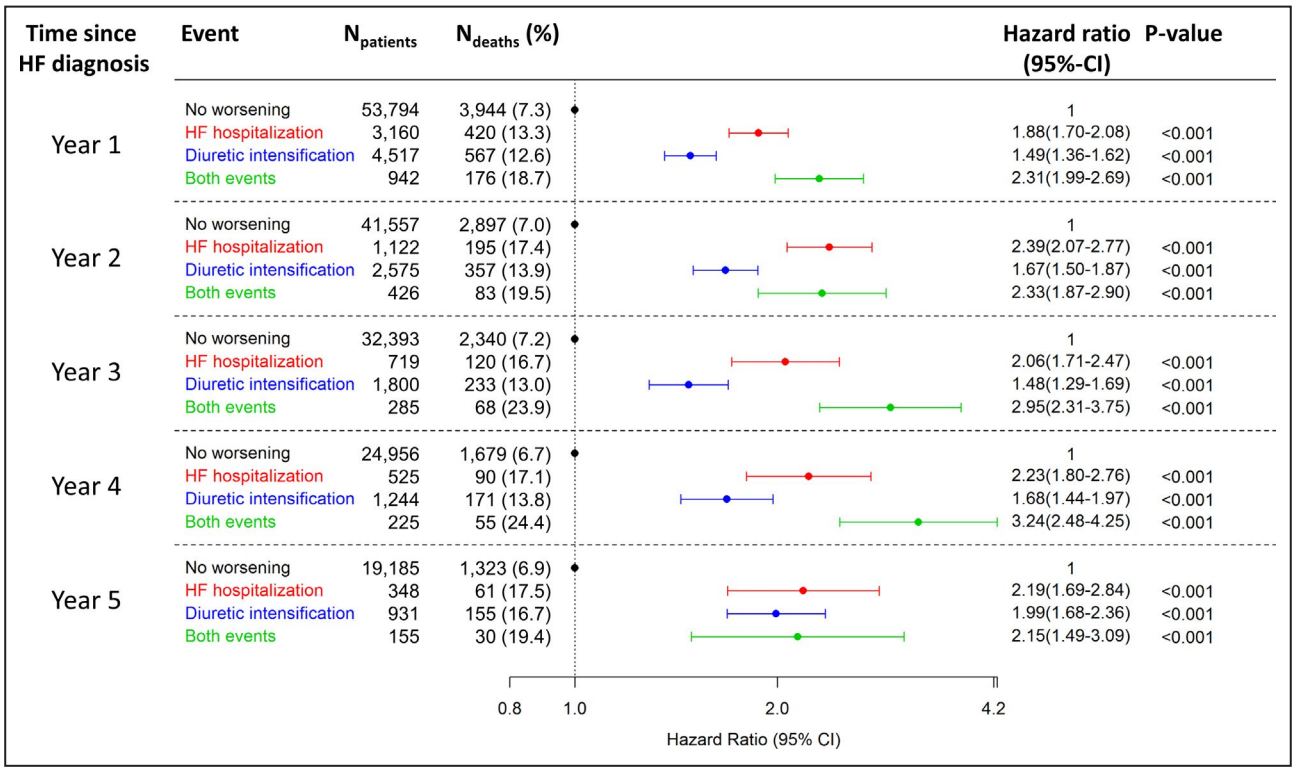

Figure 3. Hazard ratios of 1-year mortality after first intensification event, heart failure (HF) hospitalization, or both, according to time since HF diagnosis.

Patients with a worsening event 1 year are not included in the analyses for subsequent years. The multivariable Cox models are conducted at the end of each year, which is why patients have to survive until then to be included in the analyses. N_{deaths} indicates how many patients die within 1 year and the corresponding percentage of $N_{patients}$; and $N_{patients}$, number of patients in each group.

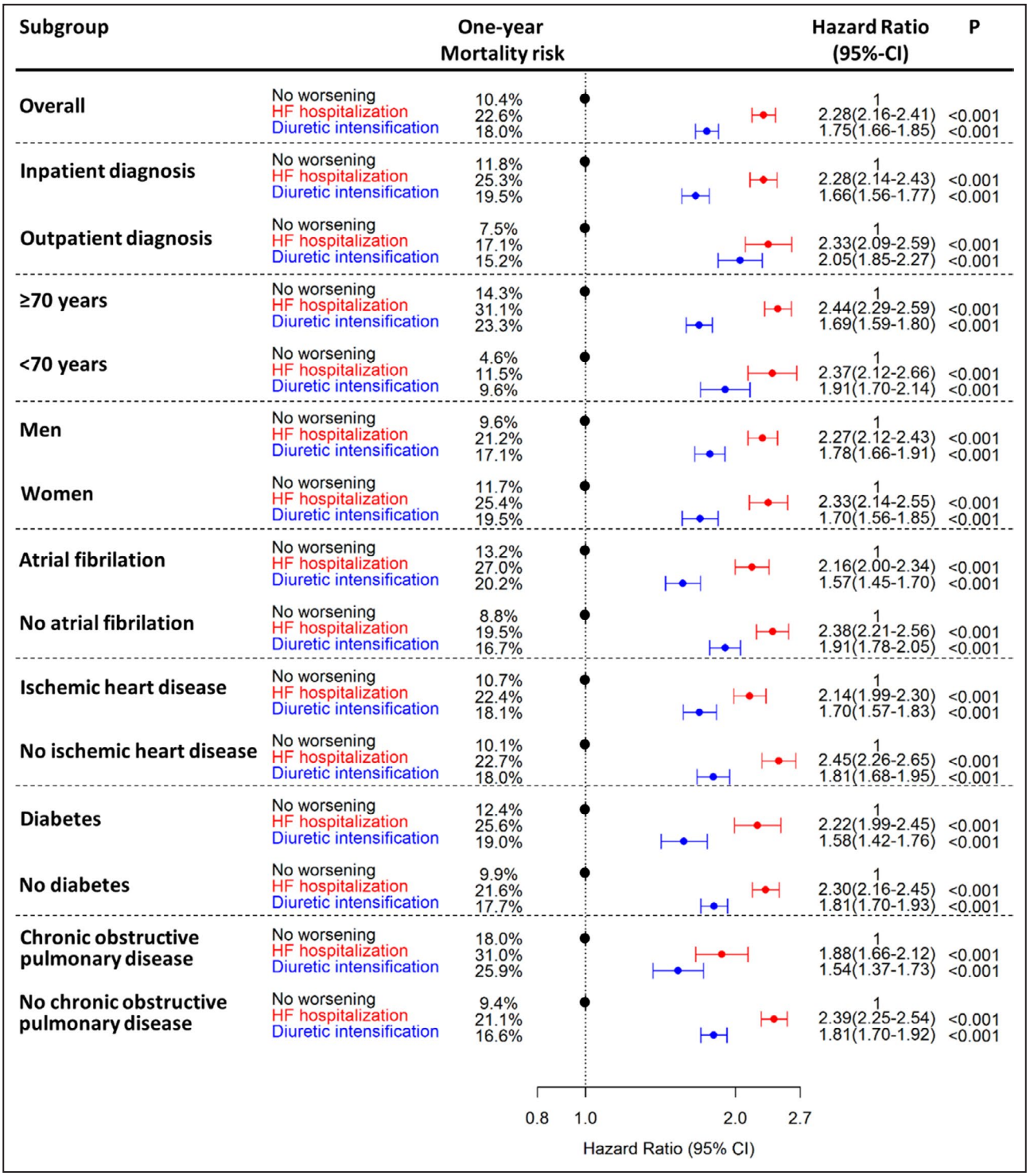

Figure 4. Absolute risk of 1-year mortality and hazard ratios after first intensification event or heart failure (HF) hospitalization compared with age- and sex-matched controls from the risk set in important subgroups.
The multivariable Cox models are conducted immediately after the worsening events, and all patients with a worsening event are included.

increased mortality was not always preceded by HF hospitalization. During 5 years of follow-up, 84.1% of the patients with an intensification event had at least one hospitalization subsequently: 20.6% had a HF hospitalization, 41.3% had a non-HF cardiovascular hospitalization, and 76.6% had a noncardiovascular hospitalization. Among patients with a HF hospitalization as first event, 88.6% had at least one more

hospitalization: 50.1% HF, 45.6% non-HF cardiovascular, and 75.4% noncardiovascular.

In an exploratory mortality analysis, we subdivided intensification events into types of intensification, also including initiating 40-mg/d furosemide equivalent (as opposed to the other analyses). All intensification event types were associated with increased mortality compared with the matched controls, except for initiating 40-mg/d furosemide equivalent, where no difference was observed (Figure S2).

DISCUSSION

Main Findings

In this nationwide cohort study, we observed that an outpatient intensification event was associated with a significantly increased mortality risk compared with patients with no signs of worsening. The risk associated with an intensification event was slightly lower compared with HF hospitalization, but outpatient intensification was a common scenario and occurred more frequently than HF hospitalizations.

Previous Studies

Our results differed from what Okumura et al observed in the PARADIGM-HF trial population,[3,4] where the 2 modes of HF worsening were equally frequent. In the present study, we registered patients with intensification events regardless of dosage maintenance (as opposed to the PARADIGM-HF trial, where changes had to be maintained for a month, which may have led to a lower incidence in that study). This may also partially explain why we observed a lower mortality risk associated with outpatient diuretic intensification events compared with HF hospitalization. When including temporary changes (eg, <30 days), it is likely that some of these events, especially in the early phase of HF, reflect up titration of guideline medical therapy, device implantation, or both rather than actual HF progression. This is supported by the outpatient event-associated increase of mortality hazard ratio the longer the time since diagnosis. Furthermore, intravenously administrated diuretic therapy was not included in the definition of outpatient intensified diuretic therapy in the present study; we only obtained data on oral therapy, because diuretic therapy is rarely administered intravenously in outpatient settings in Denmark. Such an event would, therefore, either be registered as a HF hospitalization (if lasting for a minimum of 2 days) or not be registered at all. Finally, Okumura et al[3] had more clinical information about the included patients and were able to deal with residual confounding in more comprehensive ways than in this study, which may be a part of the explanation as well.

Although annual mortality for national HF populations is often described as one aggregate rate, the current analyses further emphasize that these survival statistics represent the homogenization of different populations with different outcomes. To improve outcomes and individualize care requires accurate clinical reclassification when new events, such as intensification of therapy, have occurred. However, it is notable that the selection of patients for matching to the intensification group herein identified a group with a high 1-year mortality of 10.4%, even without history of intensification or hospitalization. Previous work in the Danish population has demonstrated a 5-year mortality of only 14% in patients selected for age <70 years and absence of noncardiac diagnoses at the time of HF diagnosis.[11]

We observed some differences between patients who, within the first year, had an intensification event and a HF hospitalization. Patients with an intensification event were slightly older and more frequently living in a nursing home, which may suggest that the threshold for hospital admission is higher among the frailest patients who are already in a facility with access to some care. Furthermore, the mechanisms behind the transition from well-compensated HF to acute decompensation are complex and remain obscure. Not all patients gain weight to any significant degree before hospital admission.[12] It has been suggested that patients with HF may have impaired ability to inhibit sympathetic activation on increasing cardiac filling pressures, which may lead to a more drastic redistribution of volume from the venous reservoir to the effective circulatory system and, thus, lead to congestion without increased bodyweight.[13,14] By closely monitoring hemodynamics, it has been possible to detect changes weeks before a HF event, and with early medical intervention, to reduce hospitalization rates.[15–17] These hemodynamic changes were also detected in patients who did not gain weight.[18]

Whether the increased mortality associated with an outpatient intensification event, observed in the present study, is attributable to the intensified diuretic therapy itself or rather the patients' need of intensification cannot be answered by the data. Although it might be explained by hypokalemia after intensification,[19] it seems more likely that the intensification is a marker of clinical instability, which confers the increased risk.[6] In an observational cohort study, use of loop diuretics, and especially higher doses, was associated with more evidence of congestion, more diabetes mellitus, and worse renal function as well as higher age. Higher doses of loop diuretics were associated with increased risk of outcomes, but in a fully adjusted model, it was not an independent predictor,[20] suggesting that higher doses could be interpreted as a sign of more advanced features of HF and congestion. In a recent randomized trial,

withdrawal of loop diuretics in a cohort of clinically stable patients with mild HF did not alter patient-reported dyspnea on the short-term.[21] Moreover, the secondary outcome of HF-related events was similar between patients who maintained or discontinued diuretic therapy, although these events were relatively infrequent. Given that the use loop diuretics itself has an effect on adverse outcomes, a difference in HF-related events would have been expected. Nevertheless, the high incidence of intensification events and the associated increased mortality risk in the present study bring up serious concerns about whether the patients are being properly evaluated. In Denmark, when a patient has received a HF diagnosis, the patient will usually attend a specialized HF clinic to initiate evidence-based medical and device therapy. When receiving relevant therapy and in stable condition, the patient is referred back to his/her primary care physician without further follow-up in the HF clinic.[22] An intensification event after this initial period will, therefore, often be managed by a primary care physician, who may not have the same awareness for potential rereferral for a thorough HF evaluation as a cardiologist. On the basis of our data, it is not possible to determine the severity of progression, but it is likely that some patients with intensification events are progressing to stage D HF,[7] without sufficient evaluation of exacerbating factors that could be addressed. Even if the trend cannot be reversed, evaluation for advanced therapies should be considered before patients have progressed to kidney and liver dysfunction, or palliative interventions may be appropriate. It is widely recognized that discussions to revise goals of care do not happen soon enough; some may be appropriately triggered by continued escalation of diuretics.

Subgroups

In subgroup analyses, we observed results like the overall population. However, for patients with an initial outpatient diagnosis of HF, patients aged <70 years at time of diagnosis, and patients with COPD at baseline, we observed no significant difference in 1-year mortality hazard after the 2 worsening events. Statistically, this is explained by broad CIs as a result of few events. It is likely that because of a high "baseline survival probability" among younger patients, this group is more affected by a worsening event than elderly patients. At the same time, younger patients may have a lower threshold for hospitalization attributable to a higher activity level and may therefore be hospitalized with less severe episodes compared with elderly patients, although this remains speculative. On the other hand, a poor baseline survival probability may be associated with less relative impact of HF worsening on mortality, as seen among patients with COPD. The results of the present study do not indicate that worsening HF should be managed differently in the different subgroups.

Limitations

As the present study was conducted using data from administrative registers, some inherited limitations prevail. We recognize that the study population represents a selected group of patients with HF, in that we have excluded the frailest patients who did not survive the initial 120 days or did not start or tolerate ACEI/angiotensin receptor blocker, β blockers, or both and, thus, the results may not be applicable for patients experiencing events early after their HF diagnosis. The absence of data on left ventricular ejection fraction is a significant limitation, as analyses stratified for left ventricular ejection fraction would be valuable in evaluating patient characteristics and worsening trajectories. We acknowledge that our results are limited by the lack of data on clinical signs and laboratory results, which could have made more comprehensive adjustment and further stratified analyses possible. We chose to define intensification events by certain jumps in dosage, based on both clinical practice (1) initiating furosemide-equivalent therapy with 80 mg/d, usually administered as 40 mg twice daily, and adding thiazide diuretic therapy when furosemide becomes insufficient and (2) doubled dosage, on the basis of the DOSE (Diuretic Optimization Strategies Evaluation) trial protocol.[23] We acknowledge that these dosage jumps are still relatively arbitrary, and other dosages could have been chosen and this would likely influence the results. Despite these limitations, the systematic enrollment and follow-up of this large population and the high positive predictive value of the HF diagnosis in the Danish registers[9] provide unique data that add the important perspective of a nontrial population.

CONCLUSIONS

Among patients with HF and ACEI/angiotensin receptor blocker and β-blocker therapy at 120 days after diagnosis, outpatient diuretic intensification events were frequent and were associated with a significantly elevated mortality risk. Although HF hospitalization was associated with an even higher risk, patients with an outpatient intensification event should receive as careful a reevaluation for optimization of drug therapy and consideration of advanced options as patients who are hospitalized for worsening HF.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Figures S1–S2

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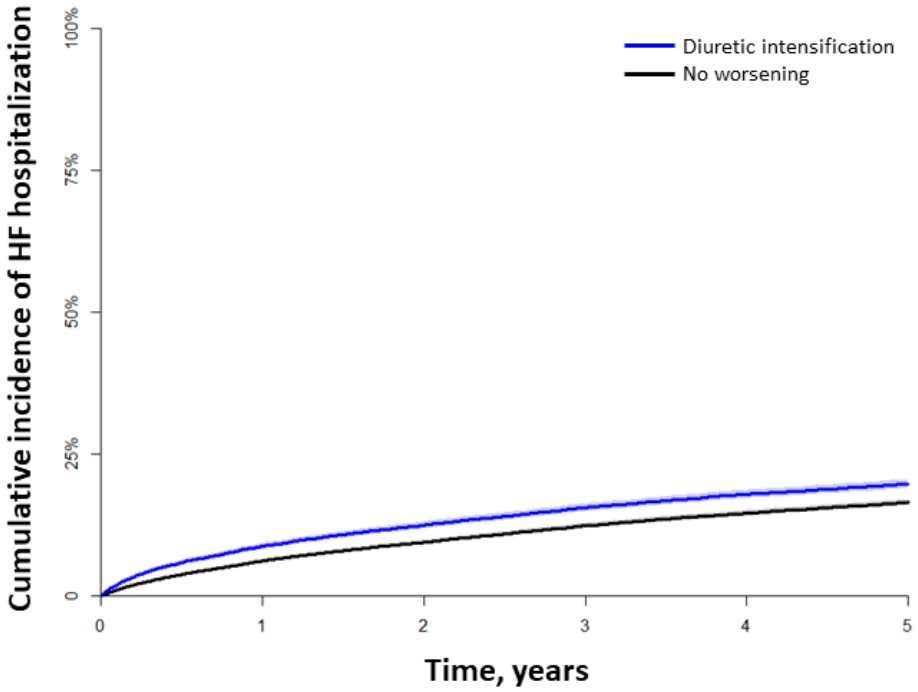
Supplemental Material

Figure S1. Competing risk analysis showing cumulative incidence of HF hospitalization after a first intensification event compared to matched controls from the risk set (a), and cumulative incidence of HF hospitalization-free mortality after a first intensification event compared to matched controls from the risk set (b).

a)



b)

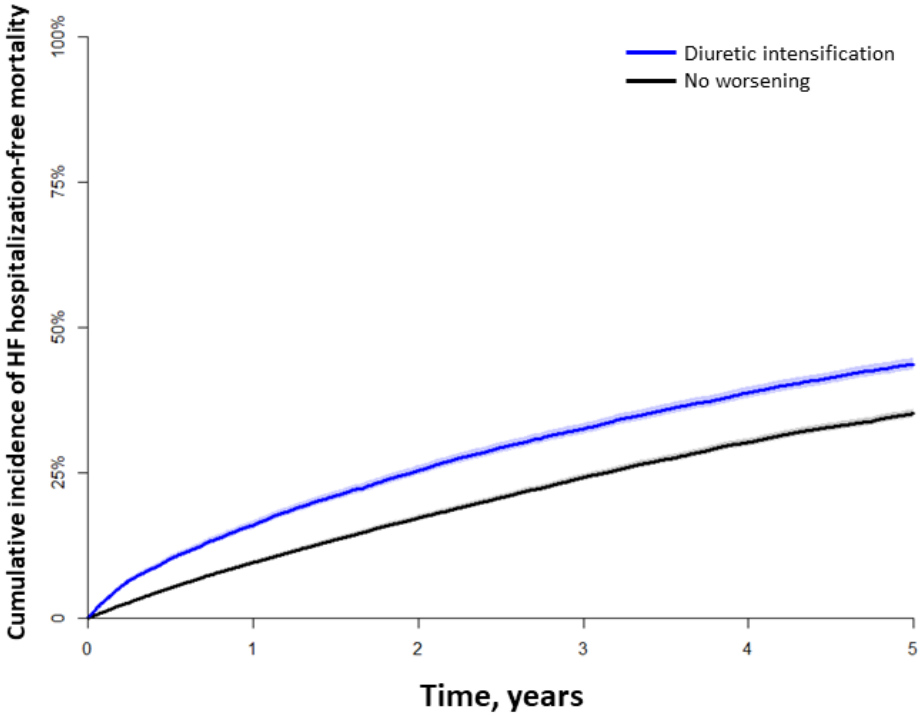


Figure S2. Cumulative incidence of all cause mortality after a first intensification event compared to matched controls from the risk set, stratified after type of intensification.

0: No intensification of diuretic therapy
1: Increased furosemide equivalent from 0 mg/day to 40mg/day (Not included in main analyses)
2: Increased furosemide equivalent from 0 mg/day to 80mg/day
3: Doubled dosage of furosemide equivalent to a minimum of 160mg/day
4: Thiazide diuretic therapy added to a minimum of 160mg/day furosemide equivalent