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ORIGINAL RESEARCH

Excess Risk of Mortality and Hospitalization in Patients with Heart Failure According to Age and Comorbidity – A Nationwide Register Study

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Background: Heart failure (HF) is associated with increased risk of death and a hospitalization, but for patients initiating guideline directed medical therapy, it is unknown how high these risks are compared to the general population – and how this may vary depending on age and comorbidity.

Methods: In this retrospective cohort study, we identified patients diagnosed with HF in the period 2011–2017, surviving the initial 120 days after diagnosis. Patients who were on angiotensin converting enzyme inhibitor (ACEi)/ angiotensin receptor blocker (ARB) and beta-blocker were included and matched to 5 non-HF individuals from the background population each based on age and sex. We assessed the 5-year risk of all-cause death, HF and non-HF hospitalization according to sex and age and baseline comorbidity.

Results: We included 35,367 patients with HF and 176,835 matched non-HF individuals. Patients with HF had a five-year excess risk (absolute risk difference) of death of 13% (31% [for HF] – 18% [for non-HF]), of HF hospitalization of 17% and of non-HF hospitalization of 24%. Excess risk of death increased with increasing age, whereas the relative risk decreased - for women in their twenties, the excess risk was 7%, risk ratio 7.2, while the excess risk was 18%, risk ratio 1.5 for women in their eighties. Having HF as a 60-year old man was associated with a five-year risk of death similar to a 75-year old man without HF. Further, HF was associated with an excess risk of non-HF hospitalization, ranging from 8% for patients >85 years to 30% for patients <30 years.

Conclusion: Regardless of age, sex and comorbidity, HF was associated with excess risk of mortality and non-HF hospitalizations, but the relative risk ratio diminishes sharply with advancing age, which may influence allocation of resources for medical care across populations.

Keywords: heart failure, excess risk, mortality, hospitalization

Introduction

The global burden of heart failure (HF) remains significant. While survival has improved in past decades due to the development of effective therapy, HF is still associated with considerable risk of premature death[1] and reduced quality of life.[2] HF readmission rates remain unacceptably high[3,4] and the cost of HF care is expected to increase.[5,6] However, the excess risk of death and hospitalization for patients with HF compared to the general population has, to our knowledge, not been quantified.

Patients with HF constitute a heterogeneous population and the excess risk of death and hospitalization associated with HF may vary according to age and comorbidity burden. To guide and treat patients and for planning future trials, knowledge on how the excess risk varies according to patient characteristics is important. Indeed, quantitative information on the expected higher mortality in HF patients compared with the background population may help physicians to understand the risk

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associated with HF compared to eg risk associated with aging or the risk of having HF in addition to severe comorbidities like diabetes, cancer and chronic obstructive pulmonary disease. For the patients, knowledge on the excess risk associated with HF is important to understand the potential impact the HF diagnosis may have on their life in comparison with their peers.[7] Finally, knowledge on risk variations may be an important tool for health care organizers to increase the focus on prevention of HF exacerbations and optimized allocation of health care resources and post-discharge care.

Therefore, in this study, we sought to estimate the excess risk of death, HF hospitalization and non-HF hospitalization in patients with HF treated with angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) *and* beta-blocker compared to age- and sex matched controls and how this varied according to age and non-cardiac comorbidities.

Methods

Data Sources

The study was a retrospective cohort study conducted using data from nationwide administrative Danish registers, including the Civil Registration Register, holding information on birth, death, migration status, the National Patient Register, holding information on all hospital in- and outpatient contacts coded due to the International Classification of Diseases 10th edition (ICD-10) and the Database of Medicinal Product Statistics, holding information on all medical prescriptions collected in Danish pharmacies. Due to the Danish person identification system, all of these registers can be combined, and individual level data can be obtained.[8]

Study Population and Outcomes

We identified all patients with a first-time HF diagnosis (ICD-10: I50) in the period 2011–2017. The patients were included if they were 18–95 years at time of diagnosis, survived the initial 120 days after the diagnosis and collected prescriptions on ACEi/ARB *and* beta-blocker in this period. This method was to ensure a population with chronic HF with a high proportion of HF with reduced ejection fraction (HFrEF).[9] At the time of inclusion (baseline: HF diagnosis + 120 days) each patient was age- and sex matched to five individuals from the risk set – ie individuals of the general population who were alive and without HF at the time of matching. The study population were followed for up to 5 years, until the end of 2017, death or emigration, whichever came first. Outcomes of interest were death, HF hospitalization and non-HF hospitalization. Further, we assessed the burden of hospitalization in terms of number of hospitalizations, duration of hospitalization and total number of days hospitalized. We used the term *excess risk* to describe the absolute risk difference.

Baseline Comorbidity and Subgroup Analyses

Baseline comorbidity was defined according to ICD-10 diagnoses as minimum one hospital contact within 5 years prior to baseline. In each subgroup analysis for non-cardiac comorbidity (diabetes, chronic obstructive pulmonary disease [COPD] and cancer), patients with HF with and without the respective comorbidity were re-matched to individuals from the risk set with and without the respective comorbidity, based on age, sex and year of comorbidity incidence (for with-comorbidity groups). Re-matching in this manner was performed to ensure that distributions of age and sex would remain consistent between patients with HF and controls. For the cancer subgroup, we further descriptively assessed the distribution of different types of cancer in patients with HF and controls, respectively.

Statistical Analyses

Baseline characteristics were presented as number and percentage for categorical variables and as median and inter-quartile range for continuous variables. The included patients with HF were age- and sex matched to 5 randomly selected controls each, using risk set matching, meaning that a person in the Danish background population was eligible as a potential match if he or she was alive and free from HF at the time of matching. Five-year mortality risk was assessed using the Kaplan–Meier estimator, while the 5-year risk of hospitalization (HF and non-HF) were assessed using the Aalen Johansen estimator. *Excess risk* was defined as the absolute risk difference between patients with HF and non-HF

controls. The level of statistical significance was set to 5%. All data management, analyses and figures were conducted in SAS version 9.4 and R version 3.5.[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 Protection Agency (project no. P-2019-262).

Results

Study Population

We identified 76,095 patients with a first-time HF diagnosis from 2011 to 2017. After excluding 11,914 who died during the initial hospital stay or during the 120 days after discharge, and 28,814 who were not in ACEi/ARB and beta-blocker therapy, we included 35,367 patients, who were matched to 176,835 non-HF controls (Figure 1). The median age was 71 and the study population consisted of 35% women. At baseline, 12,189 (34%) patients were in MRA therapy (Table 1). Both cardiovascular- and non-cardiovascular comorbidity at baseline were more frequent in the HF group than in the control group. Among the patients with HF, almost half of the patients had ischemic heart disease compared to 5% of the matched population. One-third of the patients with HF had atrial fibrillation compared to 4% of the matched population. Diabetes was twice as frequent among patients with HF (10% vs 2%) and even a non-cardiovascular disease as COPD was present in 10% of the patients with HF compared to 2% of the matched population.

Outcomes in the Overall Population

Compared to non-HF controls, HF was associated with increased 5-year risk of death (30.8% vs 17.6%, absolute risk difference 13.2, risk ratio 1.75), HF hospitalization (18.5% vs 1.5%, absolute risk difference 17.0, risk ratio 12.33) and non-HF hospitalization (72.9% vs 48.8%, absolute risk difference 24.1, risk ratio 1.49) *(illustrated in* Figure 2).

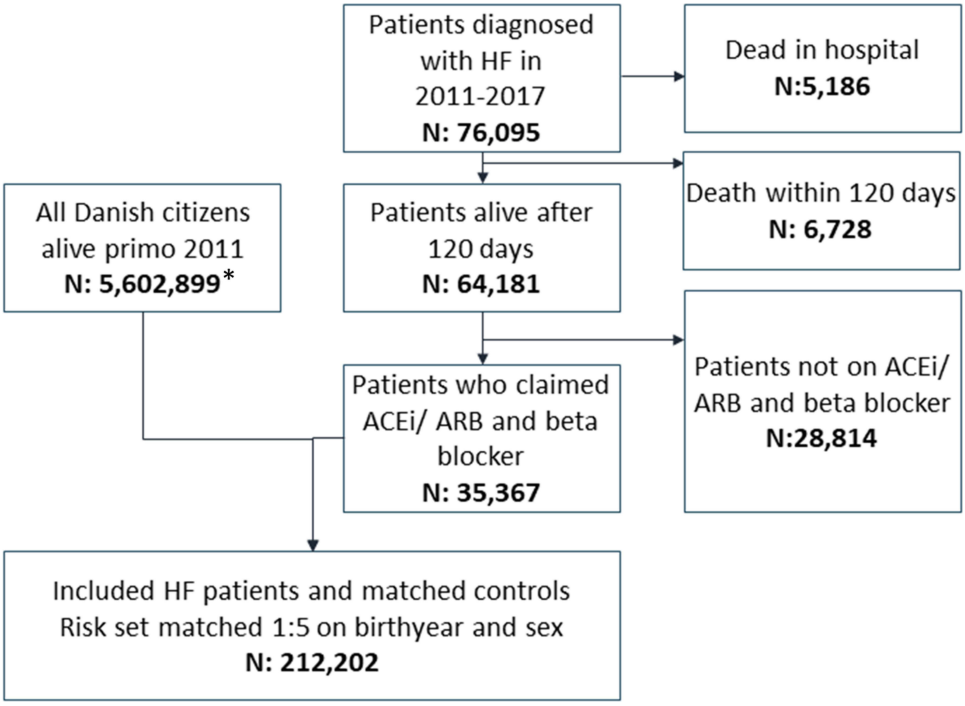

Figure 1 Selection of study population. *Potential matches - individuals from the background population could only be included as an actual match if they were free from heart failure at the time of matching.

Abbreviations: ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; HF, heart failure.

Table 1 Baseline Characteristics of the Study Population

	HF patients (35,367)	Matched Controls (176,835)
Age, median (IQR)	71 (62-79)	71 (62-79)
Female sex, n (%)	12,204 (35)	61,020 (35)
Ischemic heart disease	15,766 (45)	8443 (5)
-Myocardial infarction	9342 (26)	2611 (1)
Atrial fibrillation	12,238 (35)	7550 (4)
Stroke	2879 (8)	6798 (4)
Diabetes	6922 (20)	16,616 (9)
Chronic obstructive pulm. dis.	3670 (10)	4333 (2)
Chronic renal failure	1235 (3)	1119 (1)
Cancer	2653 (8)	9063 (5)
ACEi/ ARB	35,367 (100)	54,300 (31)
-Sacubitril/ Valsartan	35 (0)	0 (0)
Beta-blocker	35,367 (100)	28,274 (16)
MRA	12,189 (34)	2514 (1)
Loop diuretics	23,157 (65)	11,687 (7)
Thiazide diuretics	4352 (12)	19,537 (11)
Digoxin	6544 (19)	3075 (2)
Aspirin	19,632 (56)	33,378 (19)
Statin	21,806 (62)	48,635 (28)
Warfarin	8554 (24)	7631 (4)

Age-Stratified results

In the age-stratified analyses, illustrated in Figure 3, we observed that the five-year absolute risk of death increased with increasing age, but this increase was faster within the HF population, resulting in an increasing absolute risk difference with increased age (Figure 3a). This was observed for both men and women. The figure further illustrates that due to the increase in absolute risk of death the relative risk decreases with increasing age. For example, for women in their twenties, the excess risk was 7%, risk ratio 7.2, while the excess risk was 18%, risk ratio 1.5 for women in their eighties. The figure also shows that for the part of the population under 65 years, the five-year absolute mortality risk is higher among female HF patients than male patients. The risk of HF hospitalization was relatively consistent in all ages, with a slight increase in risk from 65 years and up (Figure 3b). The excess risk of non-HF hospitalization observed in the overall analysis persisted in all ages. The absolute risk difference was largest among the younger patients, and both the absolute risk difference and the risk ratio decreased with increasing age (Figure 3c).

Subgroups of Non-Cardiac Comorbidity

The overall findings of HF-associated excess risk of death and HF hospitalization were consistent regardless of baseline comorbidity-status (Figure 4). For patients with HF, baseline comorbidity had minimal impact on the five-year absolute risk of HF hospitalization. An excess risk of non-HF hospitalization was observed in all subgroups. This was found for patients with and without diabetes and patients with and without cancer with a magnitude close to that for patients with neither cancer nor COPD. The only comorbidity for which the excess risk of non-HF hospitalization was small was COPD, as the hospitalization rates for patients with COPD without HF was high. Importantly, in the subgroups without diabetes, COPD or cancer, respectively, the absolute risk differences for non-HF hospitalization were greater than for HF hospitalization (Figure 4).

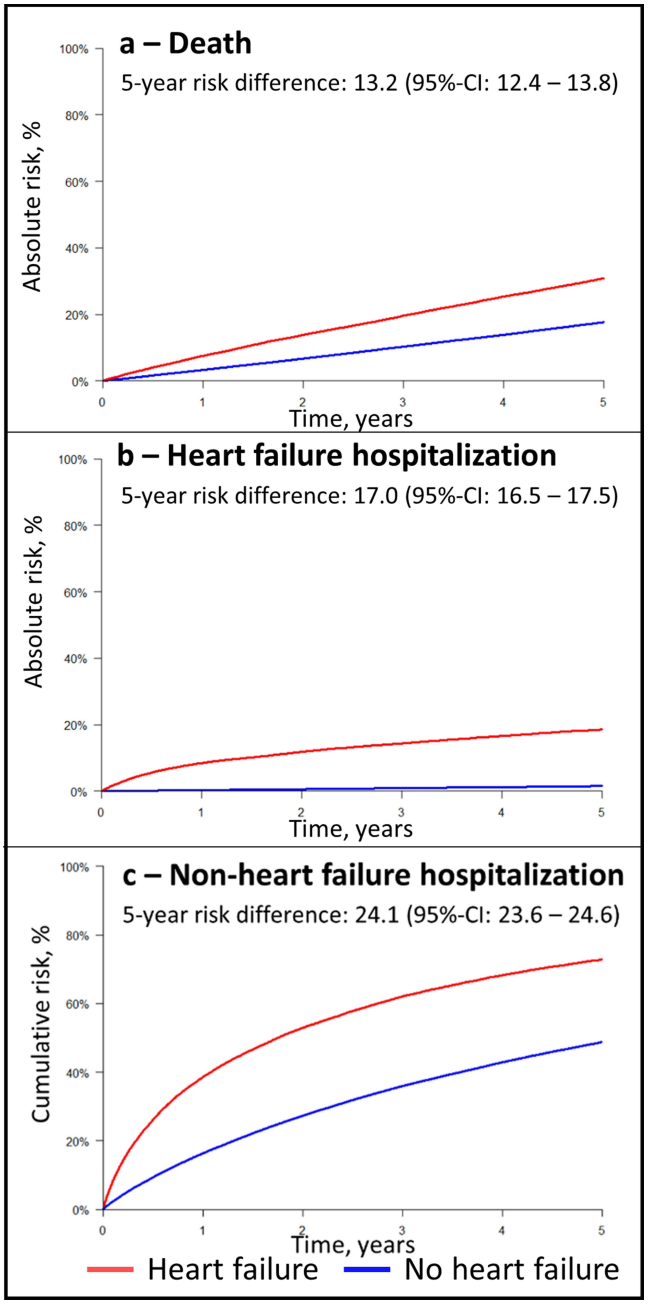

Figure 2 Cumulative incidence of death from any cause (**a**), heart failure hospitalization (**b**) and non-heart failure hospitalization (**c**) for patients with heart failure (red lines) and their matched controls (blue lines) and 5-year absolute risk differences for each outcome.

Hospitalizations

Among individuals who had at least one hospitalization (HF *or* non-HF hospitalization) during follow-up, the median number of hospitalizations was 2 (Q1-Q3: 1–4) for patients with HF and 2 (Q1-Q3: 1–3) for matched controls – a significant difference though, P <0.001, due to a different distribution with more patients with HF with a high amount of hospitalizations. Number of days hospitalized was 9 (Q1-Q3: 3–24) for patients with HF and 7 (Q1-Q3: 2–17) for matched controls (P < 0.001). The median duration of a hospitalization was 3 days (Q1-Q3: 1–7) with no significant difference between patients with HF and matched controls (P = 0.18).

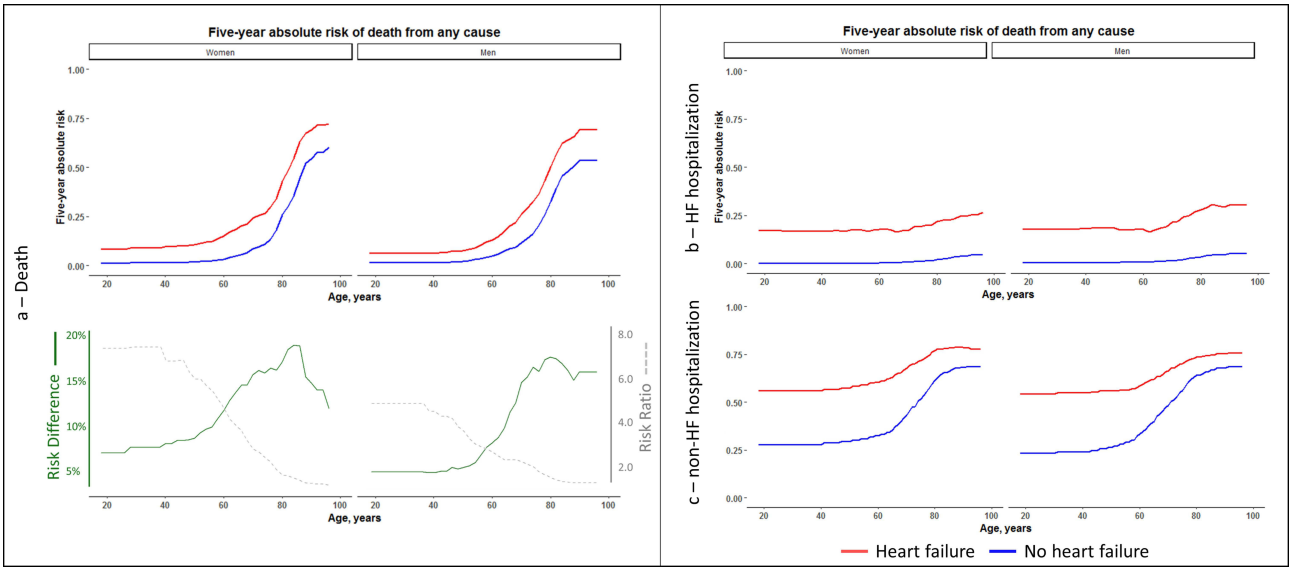

Figure 3 Age-stratified risk analyses. (**a**), above: Five-year absolute risk of death from any cause for patients with heart failure (red lines) and their matched controls (blue lines) according to age for women and men respectively. Below, the corresponding absolute risk differences (green lines) and relative risk ratios (gray dotted lines) are illustrated. (**b** and **c**): Five-year absolute risk of heart failure hospitalization (**b**) and non-heart failure hospitalization (**c**) for patients with heart failure (red lines) and their matched controls (blue lines) according to age for women and men respectively.
Abbreviation: HF, heart failure.

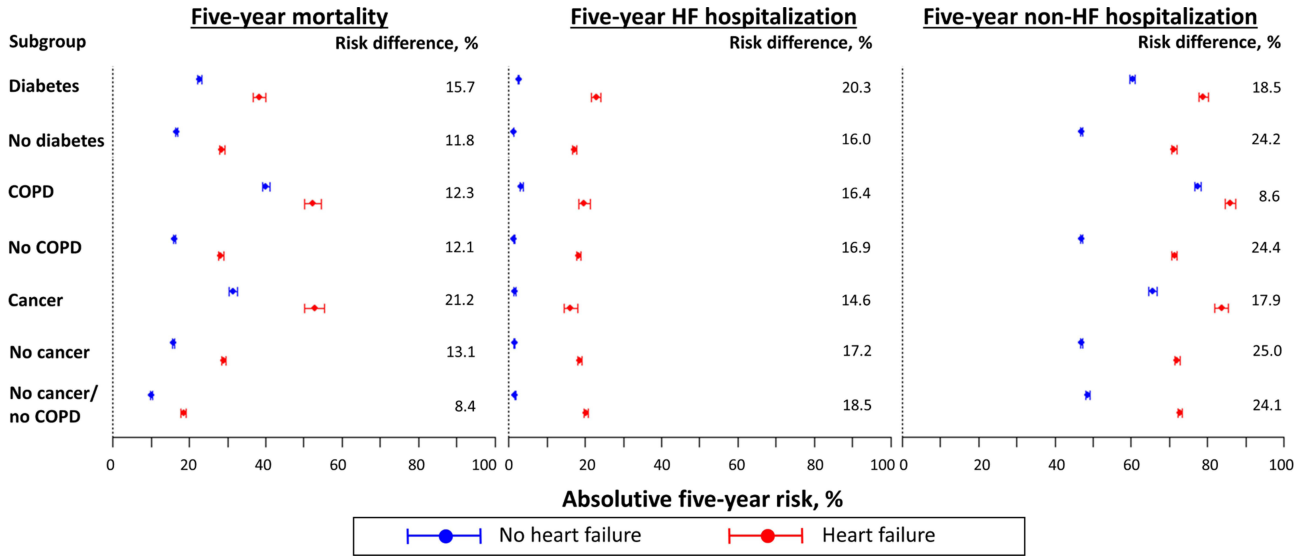

Figure 4 Five-year absolute risk of death from any cause (left), heart failure hospitalization (mid) and non-heart failure hospitalization (right) for patients with heart failure (red dots) and their matched controls (blue dots) with 95% confidence intervals according to baseline comorbidity with the corresponding absolute risk difference for each subgroup.
Abbreviations: COPD, chronic obstructive pulmonary disease; HF, heart failure.

Discussion

In this nationwide study, patients with HF who received an ACEi/ARB and beta-blocker 120 days after their first HF diagnosis had significantly increased risk of death and HF hospitalization compared to age- and sex matched non-HF individuals, in all age groups and regardless of sex and non-cardiac comorbidity. An increased risk of non-HF hospitalization associated with HF was found in all ages, although declining with increasing age. The excess risk of non-HF hospitalization was higher than the risk of HF hospitalization and was observed for patients with and without diabetes, with and without cancer but was small among patients with concomitant COPD.

Risk of Death and HF Hospitalization

We observed lower five-year mortality than in previous epidemiological studies.[11–14] The reason for this is likely the selection of patients surviving the initial vulnerable phase, presumably stabilized and initializing guideline directed medical therapy. Compared to recent trial data, we observed a slightly higher mortality among the patients with HF, and a slightly lower risk of HF hospitalization.[15,16] An older population (median age 71 years compared to 64 years in PARADIGM-HF and 66 years in DAPA-HF) likely explains this. Further, elevated natriuretic peptides or a recent HF hospitalization as a criterion for participation in recent trials may explain the higher risk of HF (compared with other) hospitalizations. In addition, patients who become asymptomatic (NYHA I) on diuretic therapy early after being diagnosed will not be included in a randomized trial but may very well appear in the present study cohort.

We observed that the risk of death was strongly age-dependent with an S-shaped relation between the five-year absolute risk of death and aging in the background population that was shifted upwards for patients with HF in an almost parallel manner, so that the excess risk remained among the older patients. In fact, the five-year absolute risk difference increased with increasing age. However, due to increasing absolute risk estimates in both groups, the relative risk ratio decreased with increasing age. The HF-related risk increased most steeply between age 60 and 80, but still, a 60-year old male patient with HF had the same mortality risk as a 75-year old without HF. For patients with HF, the absolute risk of HF hospitalization was close to similar for men and women and relatively consistent in all ages with only a minor increase from 70 years and up.

The five-year absolute risks of death varied depending on comorbidity status at baseline, with the highest risks observed in the subgroups of patients with COPD and cancer, respectively. The absolute risk difference in the cancer subgroup was more pronounced than in the main analysis. It is likely that cancer complicated by HF reflects more severe illness and that these patients are more often too fragile to undergo curative surgery and/ or chemotherapy. Neither COPD nor cancer seemed to influence the risk of HF hospitalization for patients with HF at baseline, which could imply that the excess risk of death in these subgroups are mainly non-cardiovascular.

For patients with diabetes, HF was also associated with a higher risk of death than in the main analysis. We further observed a slightly increased five-year risk of HF hospitalization in the presence of diabetes. These associations suggest an unfavorable synergetic interaction between diabetes and HF, which have been described previously both in population-based studies and in trial populations.[17,18] Besides diabetes being an independent risk factor for developing HF, some oral antidiabetic agents have been associated with increased risk of HF hospitalization.[19] In contrast, novel therapies like sodium glucose co-transporters-2 inhibitors and glucagon-like-peptide-1 agonists have shown cardio protective properties.[20–25] With an expected more aggressive implementation of these drugs in the future, it seems likely that less patients with diabetes will develop HF and that those who do will have less severe HF.

Risk of Non-HF Hospitalization

We observed an excess risk of non-HF hospitalization associated with HF regardless of age, sex and comorbidity. This outcome has rarely been described in detail although it has been described that patients with HF are often hospitalized due to comorbidity.[26,27] However, the age-associated increase was more pronounced among the non-HF matches than among patients with HF, resulting in a decreasing absolute risk difference with increasing age as opposed to the association between aging and risk of death. Since hospitalizations due to some common non-cardiac conditions such as renal failure and pneumonia are associated with impaired survival among patients with HF,[28,29] it would be highly relevant to focus on non-HF hospitalization as a trial outcome alongside HF hospitalization, as it is likely that some of the excess risk of death are mediated by non-cardiac incidents.[30] However, since the risk of hospitalization – regardless of HF – is relatively high, it could be informative to assess days spent in hospital rather than time-to-event analyses.

Perspectives

The most surprising findings of the present study were the excess risk of non-HF hospitalization associated with HF regardless of the presence or absence of comorbidity. However, this is in line with an increasing proportion of death among patients with HF being due to non-cardiac causes[30] and may confer a major challenge in attempting to reduce overall mortality further for patients with HF. Further research is needed to assess how much of this excess risk is due to excess morbidity versus lowered

threshold for admitting patients with known HF to hospital. Further, as a subject for future research, it remains unknown how much a non-HF hospitalization contribute to subsequent mortality risk compared to a hospitalization due to worsened HF. However, the findings underscore the importance of modifying/treating risk factors that may lead to HF. The excess risk of death and HF hospitalization associated with HF persisted through all ages, which underscores the importance of attempting to initiate and uptitrate medical therapy according to guidelines in elderly patients, as well as including elderly patients in intervention trials. The age-dependent magnitude of absolute and relative risk associated with HF will help determine the appropriate allocation of resources for HF.

Strengths and Limitations

The main strengths of the present study was the large sample size and completeness of data. Due to the Danish civil registration system, individuals can only be lost to follow up if they leave the country.

The excess risk of mortality and hospitalization observed in this study was not solely due to HF. While we have presented differences in baseline comorbidity and medicine, it is expected that there are similar differences in unmeasured risk factors such as obesity, alcohol, smoking, use of the health care and adherence to therapy for diabetes, hypertension and/or ischemic heart disease. It has previously been described that the incidence of HF and subsequent mortality is relatively high among individuals with low income and shorter education,[31,32] where cardiovascular risk factors tend to accumulate.[33] However, the purpose of this study was to describe the excess risk among patients with HF rather than the excess risk caused by HF – as the latter would likely result in an overestimation.

Selecting patients who were in ACEi/ARB and beta-blocker therapy to identify HFrEF introduced a limitation in the generalizability of the results. The method is associated with a sensitivity of 85%, meaning that we expect to have missed 15% of the patients with HFrEF.[9] It is likely that these patients were more frail than the average patient included, and thus the results would have been affected by including them. Further stratification of the results based on clinical parameters such as NYHA class, LVEF, coronary artery disease and kidney function would have been relevant. Unfortunately, we did not have access to such data.

Conclusions

Regardless of age, sex and comorbidity, we observed that patients with HF had a significantly higher risk of death and hospitalizations – HF and non-HF – compared to matched controls of same age and sex. The excess risk of death increased with increasing age, whereas the relative risk diminished sharply. The excess risk of non-HF hospitalization was bigger than the risk of HF hospitalization.

Abbreviations

ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD-10, the International Classification of Diseases 10th edition; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association classification system.

Disclosure

Professor Lars Køber reports personal fees from Speakers honorarium from Novo, Novartis, AstraZeneca and Boehringer, outside the submitted work. Professor Finn Gustafsson reports personal fees from Abbott, Novartis, Pfizer, AstraZeneca, Alnylam, and Bayer, outside the submitted work. Dr Søren Lund Kristensen reports personal fees from AstraZeneca, Bayer, outside the submitted work and is currently an employee of Novo Nordisk. Professor Christian Torp-Pedersen reports grants from Bayer and Novo Nordisk, during the conduct of the study. Professor Morten Schou reports lecture fees from Novo Nordisk, Novartis, AstraZeneca and Boehringer Ingelheim outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Glynn P, Lloyd-Jones DM, Feinstein MJ, Carnethon M, Khan SS. Disparities in cardiovascular mortality related to heart failure in the United States. *J Am Coll Cardiol*. 2019;73(18):2354–2355. doi:10.1016/j.jacc.2019.02.042
2. Hobbs FDR, Kenkre JE, Roalfe AK, Davis RC, Hare R, Davies MK. Impact of heart failure and left ventricular systolic dysfunction on quality of life: a cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. *Eur Heart J*. 2002;23 (23):1867–1876.
3. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the medicare fee-for-service program. *N Engl J Med*. 2009;360 (14):1418–1428. doi:10.1056/NEJMsa0803563
4. Ross JS, Chen J, Lin Z, et al. Recent national trends in readmission rates after heart failure hospitalization. *Circ Heart Fail*. 2010;3(1):97–103. doi:10.1161/CIRCHEARTFAILURE.109.885210
5. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American heart association. *Circ Heart Fail*. 2013;6(3):606–619. doi:10.1161/HHF.0b013e318291329a
6. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev*. 2017;3(1):7–11.
7. Banerjee P, Watson C, Ali D. Discussing prognosis in heart failure: a questionnaire-based study of the patient's view. *JACC*. 2018;6(9):803–804. doi:10.1016/j.jchf.2018.04.001
8. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541–549.
9. Madelaire C, Gustafsson F, Køber L, et al. Identification of patients with new-onset heart failure and reduced ejection fraction in Danish administrative registers. *Clin Epidemiol*. 2020;12:589–594. doi:10.2147/CLEP.S251710
10. R Development Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; 2008. ISBN 3-900051-07-0, ISBN 3-900051-07-0. Available from: http://www.R-project.org. Accessed September 17, 2024.
11. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347 (18):1397–1402. doi:10.1056/NEJMoa020265
12. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292 (3):344–350. doi:10.1001/jama.292.3.344
13. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the atherosclerosis risk in communities study). *Am J Cardiol*. 2008;101(7):1016–1022. doi:10.1016/j.amjcard.2007.11.061
14. Schmidt M, Ulrichsen SP, Pedersen L, Bøtker HE, Sørensen HT. Thirty-year trends in heart failure hospitalization and mortality rates and the prognostic impact of co-morbidity: a Danish nationwide cohort study. *Eur J Heart Fail*. 2016;18(5):490–499. doi:10.1002/ejhf.486
15. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371 (11):993–1004. doi:10.1056/NEJMoa1409077
16. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381 (21):1995–2008. doi:10.1056/NEJMoa1911303
17. Thrainsdottir IS, Aspelund T, Thorgeirsson G, et al. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. *Diabetes Care*. 2005;28(3):612–616. doi:10.2337/diacare.28.3.612
18. MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) programme. *Eur Heart J*. 2008;29 (11):1377–1385.
19. Udell JA, Cavender MA, Bhatt DL, Chatterjee S, Farkouh ME, Scirica BM. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol*. 2015;3(5):356–366. doi:10.1016/S2213-8587(15)00044-3
20. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644–657. doi:10.1056/NEJMoa1611925
21. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347–357. doi:10.1056/NEJMoa1812389
22. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392(10157):1519–1529. doi:10.1016/S0140-6736(18) 32261-X
23. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311–322. doi:10.1056/NEJMoa1603827
24. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375 (19):1834–1844. doi:10.1056/NEJMoa1607141
25. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373 (22):2117–2128. doi:10.1056/NEJMoa1504720
26. Dunlay SM, Redfield MM, Weston SA, et al. Hospitalizations after heart failure diagnosis a community perspective. *J Am Coll Cardiol*. 2009;54 (18):1695–1702. doi:10.1016/j.jacc.2009.08.019
27. Madelaire C, Gustafsson F, Kristensen SL, et al. Burden and causes of hospital admissions in heart failure during the last year of life. *JACC Heart Fail*. 2019;7(7):561–570. doi:10.1016/j.jchf.2019.03.018
28. Fonarow GC, Abraham WT, Albert NM, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med*. 2008;168(8):847–854. doi:10.1001/archinte.168.8.847
29. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure–associated hospitalizations in the United States. *J Am Coll Cardiol*. 2013;61 (12):1259–1267. doi:10.1016/j.jacc.2012.12.038
30. Cubbon RM, Gale CP, Kearney LC, et al. Changing characteristics and mode of death associated with chronic heart failure caused by left ventricular systolic dysfunction: a study across therapeutic eras. *Circ Heart Fail*. 2011;4(4):396–403. doi:10.1161/CIRCHEARTFAILURE.110.959882
31. Hawkins NM, Jhund PS, McMurray JJV, Capewell S. Heart failure and socioeconomic status: accumulating evidence of inequality. *Eur J Heart Fail*. 2012;14(2):138–146.

32. Andersen J, Gerds TA, Gislason G, et al. Socioeconomic position and one-year mortality risk among patients with heart failure: a nationwide register-based cohort study. *Eur J Prev Cardiol*. 2020;27(1):79–88. doi:10.1177/2047487319865946
33. Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the prospective urban rural epidemiologic (PURE) study. *Lancet Glob Health*. 2019;7(6):e748–60. doi:10.1016/S2214-109X(19)30045-2