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ORIGINAL RESEARCH

Temporal Trends in the Initiation of Dialysis Among Patients With Heart Failure With or Without Diabetes: A Nationwide Study From 2002 to 2016

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BACKGROUND: The incidence and distribution of acute and chronic dialysis among patients with heart failure (HF), stratified by diabetes, remain uncertain. We hypothesized that with improved survival and rising comorbidities, the demand for dialysis would increase over time.

METHODS AND RESULTS: Patients with incident HF, aged 18 to 100 years, between 2002 and 2016, were identified using Danish nationwide registers. Primary outcomes included acute and chronic dialysis initiation, HF-related hospitalization, and all-cause mortality. These outcomes were assessed in 2002 to 2006, 2007 to 2011, and 2012 to 2016, stratified by diabetes. We calculated incidence rates (IRs) per 1000 person-years and hazard ratios (HR) using multivariable Cox regression. Of 115 533 patients with HF, 2734 patients received acute dialysis and 1193 patients received chronic dialysis. The IR was 8.0 per 1000 and 3.5 per 1000 person-years for acute and chronic dialysis, respectively. Acute dialysis rates increased significantly among patients with diabetes over time, while no significant changes occurred in those without diabetes, chronic dialysis, HF-related hospitalization, or overall mortality. Diabetes was associated with significantly higher HRs of acute and chronic dialysis, respectively, compared with patients without diabetes (HR, 2.07 [95% CI, 1.80–2.39] and 2.93 [95% CI, 2.40–3.58] in 2002 to 2006; HR, 2.45 [95% CI, 2.14–2.80] and 2.86 [95% CI, 2.32–3.52] in 2007 to 2011; and 2.69 [95% CI, 2.33–3.10] and 3.30 [95% CI, 2.69–4.06] in 2012 to 2016).

CONCLUSIONS: The IR of acute and chronic dialysis remained low compared with HF-related hospitalizations and mortality. Acute dialysis rates increased significantly over time, contrasting no significant trends in other outcomes. Diabetes exhibited over 2-fold increased rates of the outcomes. These findings emphasize the importance of continued monitoring and renal care in patients with HF, especially with diabetes, to optimize outcomes and prevent adverse events.

Key Words: acute dialysis ■ chronic dialysis ■ diabetes ■ epidemiology ■ heart failure ■ hospitalization due to heart failure

In patients with heart failure (HF), renal dysfunction (ranging from mild renal impairment to end-stage kidney disease requiring dialysis treatment) constitutes an important prognostic factor for adverse outcomes such as rehospitalization and mortality.[1–3] After the introduction of sodium-glucose cotransporter

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CLINICAL PERSPECTIVE

What Is New?

- Renal dysfunction and diabetes constitute increasingly prevalent comorbidities among patients with heart failure (HF); however, although the acute dialysis rates increased significantly over time, the incidence of acute and chronic dialysis constituted a relatively minor challenge compared with HF-related hospitalization and all-cause mortality.
- After controlling for patient characteristics and comorbidities, patients with HF with concomitant diabetes displayed a more than 2-fold elevation in the incidence of both acute and chronic dialysis initiation, HF-related hospitalization, and all-cause mortality.

What Are the Clinical Implications?

- Our data clearly demonstrate that the mortality risk is much higher compared with the risk of end-stage renal disease among patients with HF with and without diabetes.
- A continued focus on the prevention of premature death in HF is therefore warranted; specifically in patients with both HF and diabetes, efforts to prevent end-stage renal disease with, eg, sodium-glucose cotransporter 2 inhibitors, are essential.

Nonstandard Abbreviations and Acronyms

ATC	Anatomical Therapeutic Chemical
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
EMPEROR-Preserved	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and Preserved Ejection Fraction
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and Reduced Ejection Fraction
KDIGO	Kidney Disease: Improving Global Outcomes
IR	incidence rate
IRR	incidence rate ratio
NOMESCO	Nordic Medico-Statistical Committee

2 inhibitors in the treatment of HF, there has been a renewed focus on the prevention of renal dysfunction in patients with HF with and without diabetes and the use of renal end points in HF trials.[4–6] Nevertheless, how common initiation of dialysis is in a large unselected HF population and the distribution of dialysis between an acute or chronic setting are not widely known. An escalation in comorbidities has been documented among individuals diagnosed with HF, owing to advancements in life expectancy.[7–9] Given these advancements in life expectancy and enhanced survival rates in patients with HF, we hypothesized that the demand for dialysis would experience a concomitant rise over time. With that in mind, as well as the enhanced life expectancy and improved survival among patients with HF, we hypothesized that the need for dialysis would increase over the years. Diabetes is a common comorbidity in patients with HF and is currently increasing in frequency, thus constituting a strong predictor for cardiovascular death and hospitalization due to HF.[10,11] In patients with diabetes without HF, diabetes has been shown to be strongly associated with an increased risk of renal dysfunction.[12,13] However, the extent to which the coexistence of diabetes is associated with an increased risk of dialysis in patients with HF has not been thoroughly investigated.

Therefore, we conducted a nationwide study to examine the incidence of acute and chronic dialysis initiation among patients with HF stratified by diabetes in time-trend analyses from 2002 to 2016. We compared the temporal trends in the incidence of dialysis with the incidence of hospitalization due to HF and all-cause mortality. We conducted this comparison to understand dialysis' relative importance in relation to traditional HF end points.

METHODS

The data utilized for the present study were obtained from Statistics Denmark. However, the data are not publicly available due to restrictions and are exclusively used under permission and license for the present study. Nevertheless, upon reasonable request and with permission from Statistics Denmark, data are accessible and can be presented.

Data Sources

At birth or immigration, every Danish citizen is assigned a personal identification number that enables linkage between nationwide registers, containing information on an individual level. For this nationwide cohort study, we obtained data from several Danish national registers, that have previously been validated for epidemiological research.[14–16] Demographic information, including data on sex, date of birth, vital

status, and migration was gathered from the Danish Civil Registration System.[14] We extracted information on diagnoses, hospital admissions, and outpatient contacts coded with a primary and optional secondary diagnosis according to the *International Classification of Diseases, Tenth Revision* (*ICD-10* since 1994), from the Danish National Patient Register.[15] Moreover, this register contains information on treatments including surgical procedures according to the Nordic Medico-Statistical Committee (NOMESCO) classification.[15,17] Information on patients' medical prescriptions redeemed at Danish pharmacies, coded according to the World Health Organization's defined Anatomical Therapeutic Chemical (ATC) classification system, was obtained from the Danish National Prescription Register.[16]

Study Population

We identified all Danish individuals, aged 18 to 100 years, with incident HF between January 1, 2002, and December 31, 2016 (Figure 1). The HF diagnosis was defined from registered *ICD* codes (DI50, DI11.0, DI42, and DJ81), which have previously been validated with high specificity and high negative and positive predictive values (Table S1).[18,19] Both overnight hospital stays for HF and outpatient clinic visits were considered. Patients who received chronic dialysis treatment prior to the HF diagnosis were excluded. A flowchart of the patients' selection criteria is illustrated in Figure 2.

Baseline Characteristics

Comorbidities of interest were defined using *ICD-10* codes and included diagnoses registered up to 5 years prior to the HF diagnosis (index date). These included diabetes, ischemic heart disease, hypertension, atrial fibrillation, transient ischemic attack, peripheral atherosclerosis, chronic obstructive pulmonary disease, cancer, and chronic kidney disease. Concurrent use of pharmacotherapy was defined from prescriptions redeemed within 180 days prior to HF diagnosis and included renin-angiotensin system inhibitors, β-blockers, mineralocorticoid receptor antagonists, loop diuretics, acetylsalicylic acid, digoxin, statins, and antihyperglycemic agents (Table). Diabetes was defined by *ICD* codes or by at least one redeemed prescription of antihyperglycemic agents (Table S1).[20] The *ICD* and ATC codes used to define the outcomes, comorbidities, and concurrent pharmacotherapy are listed in Table S1.

Outcomes

The primary outcomes of the study were acute dialysis, chronic dialysis, hospitalization due to HF, and all-cause mortality.

Acute dialysis was defined as the first-time initiation of dialysis during a hospitalization, and chronic dialysis was defined as the first-time initiation of dialysis during an outpatient setting.[21] The definition of dialysis included initiation of either hemodialysis or peritoneal dialysis according to the NOMESCO classification of surgical procedures code "BJFD." The definition of hospitalization due to HF was the first hospitalization for HF following the diagnosis of new-onset HF ie, the first hospitalization due to HF for patients diagnosed in an outpatient setting, and the first rehospitalization for HF in patients diagnosed in an inpatient setting.[22] A hospitalization lasting overnight was deemed necessary in order to eliminate minor insignificant hospital visits, which might not indicate true worsening of HF.

Patients were followed from first-time HF diagnosis to the first occurring event of either occurrence of the outcome of interest, death, emigration, end of study (December 31, 2017), or end of 5-year follow-up (Figure 1).

Statistical Analysis

Baseline characteristics for the cohort are presented as numbers with percentages for dichotomous variables and as medians with 25th to 75th percentiles (interquartile range [IQR]) for continuous variables. Patients

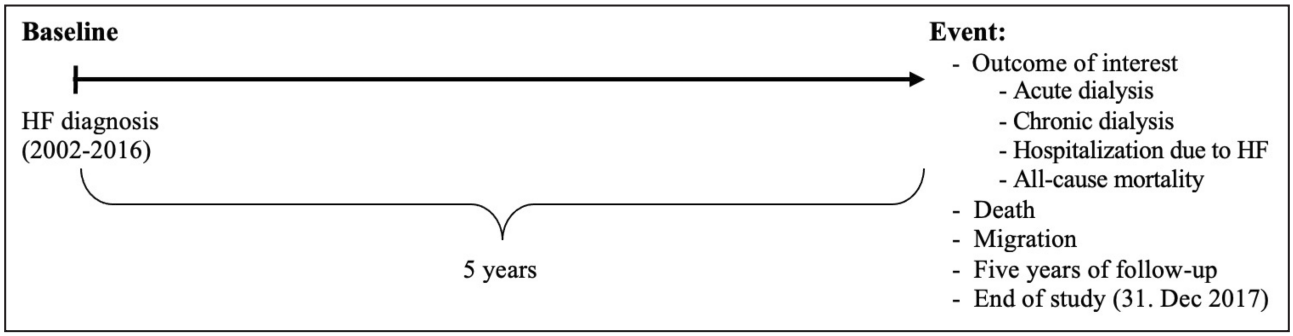

Figure 1. Study design.
The timeline illustrates the period of interest from the diagnosis of heart failure (HF) to the first occurring event of the outcomes. Thus, the baseline was set as the date of HF diagnosis.

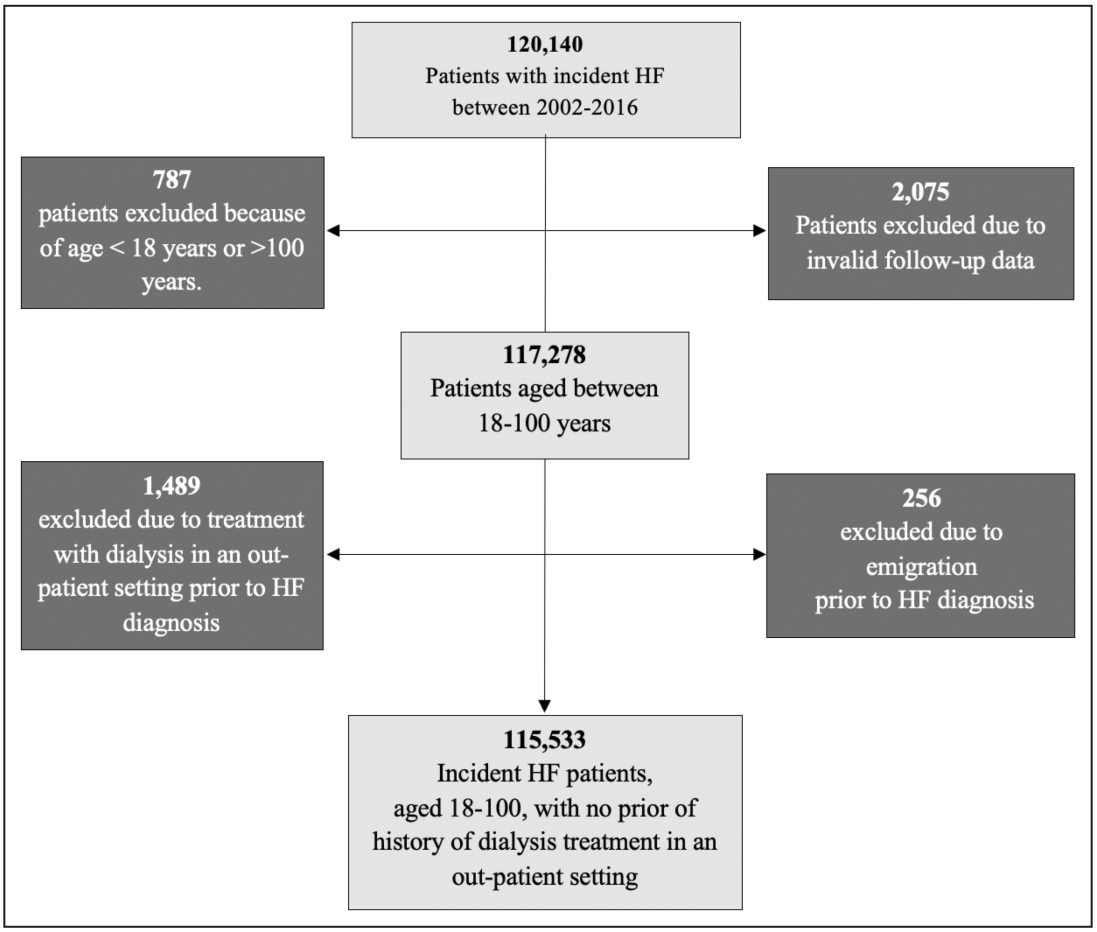

Figure 2. Flowchart of the selection criteria for the study population.
The flowchart illustrates selection criteria for the study population. Inclusion criteria of the patients with heart failure (HF) are marked by light gray boxes, while exclusion criteria are marked by dark gray boxes.

were divided into 2 separate groups "with diabetes" or "without diabetes" according to the status of diabetes at the time of HF diagnosis. The time of inclusion from 2002 to 2016 was divided into 3 time periods: 2002 to 2006, 2007 to 2011, and 2012 to 2016. In each time period, we calculated the crude 5-year incidence rates (IRs; number of events divided by 1000 person-years) of acute dialysis, chronic dialysis, hospitalization due to HF, and all-cause mortality, stratified by the status of diabetes. Person-years were calculated as the sum of every patient's time at risk. To compare the IRs, incidence rate ratios (IRRs; ratio between the IR) were assessed. To estimate statistical significance in temporal trends of the IR of the outcomes, we performed a linear regression model with time periods as a continuous variable. In multivariable Cox proportional hazards regression models, hazard ratios (HRs) with 95% CIs were calculated to evaluate the association between diabetes on the HR of the outcomes. For the analyses, the assumption of proportional hazards was graphically investigated, and no violations of the assumptions were observed. To control for potential confounders, Cox models were adjusted for sex, age, and history of comorbidities, including hypertension, ischemic stroke, ischemic heart disease, and atrial fibrillation. Patients with HF without diabetes served as the reference group in all analyses. Further, we tested for a potential interaction between the 3 time periods and diabetes on the rates of the 4 different outcomes.

All statistical analyses were performed with the statistical analysis programs SAS software version 9.4M2 (SAS Institute Inc.) and R version 4.0.3 (R Foundation for Statistical Computing). The level of statistical significance was set at $P<0.05$.

Supplementary Analyses

The CI of acute dialysis, chronic dialysis, hospitalization due to HF, and all-cause mortality according to the 3 time periods, within a 5-year follow-up period from the diagnosis of HF, were calculated. The risk of dialysis and hospitalization due to HF was computed using the Aalen-Johansen estimator, while the risk of all-cause mortality was estimated using the Kaplan–Meier

Table. Baseline Characteristics of Patients With Incident HF Stratified by Diabetes

	With Diabetes	Without Diabetes	Total
	(n=22 486)	(n=93 047)	(N=115 533)
Demographics			
Age (median [IQR]), y	73 [65–80]	74 [64–83]	74 [64–82]
Men	14 142 (62.9)	54 174 (58.2)	68 316 (59.1)
Comorbidities			
Diabetes	22 486 (100)	0 (0)	22 486 (19.5)
Ischemic heart disease	11 781 (52.4)	37 216 (40.0)	48 997 (42.4)
Hypertension	11 644 (51.8)	27 613 (29.7)	39 257 (34.0)
Atrial fibrillation	7334 (32.6)	29 703 (31.9)	37 037 (32.1)
Ischemic stroke	2211 (9.8)	6589 (7.1)	8800 (7.6)
Transient ischemic attack	651 (2.9)	2261 (2.4)	2912 (2.5)
Peripheral atherosclerosis	2408 (10.7)	4163 (4.5)	6571 (5.7)
Chronic obstructive pulmonary disease	3918 (17.4)	13 757 (14.8)	17 675 (15.3)
Cancer	2487 (11.1)	10 770 (11.6)	13 257 (11.5)
Chronic kidney disease	3535 (15.7)	4045 (4.3)	7580 (6.6)
Pharmacotherapy			
Renin-angiotensin system inhibitors	14 523 (64.6)	37 776 (40.6)	52 299 (45.3)
β-Blockers	10 297 (45.8)	34 230 (36.8)	44 527 (38.5)
Mineralocorticoid receptor antagonists	3333 (14.8)	9027 (9.7)	12 360 (10.7)
Loop diuretics	12 691 (56.4)	36 540 (39.3)	49 231 (42.6)
Acetylsalicylic acid	12 302 (54.7)	36 841 (39.6)	49 143 (42.5)
Digoxin	3421 (15.2)	11 497 (12.4)	14 918 (12.9)
Statins	12 758 (56.7)	26 823 (28.8)	39 581 (34.3)
Antihyperglycemics agents	18 566 (82.6)	0 (0.0)	18 566 (16.1)

Data are presented as median [interquartile range] for continuous variables and numbers (percentage) for dichotomous variables. HF indicates heart failure.

estimator. The analyses were stratified by age, and the median age at baseline was used to categorize the HF population into the groups "<74 years" or "≥74 years" (Figures S1A through S1D, S2A through S2D, S3A through S3D, and S4A through S4D).

A sensitivity analysis with differentiation of patients according to the initiation of either short- or long-term dialysis was conducted. Since 2002, it has been standard clinical protocol in Denmark to systematically record instances of acute dialysis for short-term purposes using procedure code "BJFD0." Long-term dialysis was defined as the initiation of dialysis, excluding individuals who underwent dialysis for acute reasons. Patients who received long-term dialysis prior to their HF diagnosis were excluded from this analysis. Figure S5A and S5B illustrates the calculated incidence rates per 1000 person-years of patients with HF receiving intended short- and long-term dialysis in comparison to the traditional HF end points.

A Fine-Gray sensitivity analysis was conducted to complement the reported Cox regression hazard model. This additional analysis was performed to affirm the robustness of our findings. Figure S6 illustrates the subdistribution HRs with 95% CIs of the outcomes.

Furthermore, to evaluate the impact of incident dialysis and hospitalization due to HF on survival, we assessed the 1-year mortality risk following the event, as a case fatality risk using Kaplan–Meier estimator (Figures S7A and S7B, S8A and S8B, and S9A and S9B). For this analysis, the follow-up period was set from the date of the initiation of dialysis and hospitalization, respectively, to the first occurring event of either death, migration, end of study (December 31, 2018), or end of 1-year follow-up as illustrated in Figure S10A and S10B. In addition, temporal trends in HF treatment within the first 3 months after HF diagnosis according to diabetes were analyzed in a subgroup of patients who were alive and not excluded, including renin-angiotensin system inhibitors, β-blockers, mineralocorticoid receptor antagonists, and loop diuretics (Table S2).

Ethics

Register-based studies using Danish administrative health registers do not require ethical approval, and no informed consent was required. However, the data use was approved by the responsible institute (Capital Region of Denmark, approval number: P-2019-348)

in accordance with the General Data Protection Regulation.

We used the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) cohort checklist when writing our report.[23]

RESULTS

Baseline Characteristics

We included 115 533 patients with incident HF in Denmark between 2002 and 2016, with a median age of 74 years [IQR, 64–82 years] and 41% being women (Table). Over the study period, the median age at HF diagnosis decreased (75 years [IQR, 65–83 years] to 74 years [IQR, 63–82 years] to 73 years [IQR, 63–82 years] in 2002–2006, 2007–2011, and 2012–2016, respectively), and the proportion of men (56.6% to 60.0% to 60.8%, respectively) increased slightly. From the first period (2002–2006) to the last (2012–2016), the prevalence of comorbidities increased generally, including diabetes, hypertension, atrial fibrillation, cancer, and chronic kidney disease (Table S1). At the time of HF diagnosis, diabetes was present in 22 486 patients (≈19%) of the patients with HF. Patients with HF with diabetes had a higher prevalence of both cardiovascular and noncardiovascular comorbidities, except for cancer, as well as higher utilization of pharmacotherapy at baseline compared with patients without diabetes (Table and Table S3).

Temporal Trends in the IR and HR of Dialysis

Within a median follow-up of 3.2 years (IQR, 1.1–5.0 years), a total of 2734 patients (2.4%) were treated with acute dialysis, and 1193 patients (1%) received chronic dialysis. Acute dialysis treatment was initiated by 1030 patients (4.6%) with diabetes (median follow-up of 2.69 years [IQR, 0.94–5.00 years]) and 1704 patients (1.8%) without diabetes (median follow-up of 3.34 years [IQR, 1.18–5.00 years]). Treatment with chronic dialysis occurred in 553 patients (2.5%) with diabetes (median follow-up of 2.70 years [IQR, 0.96–5.00 years]) and 640 patients (0.7%) without diabetes (median follow-up of 3.36 years [IQR, 1.19–5.00 years]). The IR of acute dialysis for patients with HF was 8.0 per 1000 person-years. In patients with diabetes, the IRs of acute dialysis were 15.5, 16.7, and 17.9 per 1000 person-years in 2002 to 2006, 2007 to 2011, and 2012 to 2016, respectively, and 6.3, 6.0, and 5.8 per 1000 person-years for patients without diabetes. The IR of chronic dialysis for HF patients was 3.5 per 1000 person-years. The IRR between acute and chronic dialysis was 2.3, thus patients with HF were more than twice as likely to receive acute dialysis compared with chronic dialysis. Among patients with diabetes, the IRs of chronic dialysis were 9.5, 7.7, and 9.8 per 1000 person-years and 2.4, 2.1, and 2.4 per 1000 person-years for patients without diabetes. Throughout all 3 time periods, the crude IR, as well as the adjusted HR of acute and chronic dialysis, were significantly higher for patients with diabetes compared with patients without diabetes (Figure 3A and 3B). HRs of acute dialysis for patients with diabetes, where patients without diabetes constitute the reference group (2.07 [95% CI, 1.80–2.39] in 2002 to 2006, 2.45 [95% CI, 2.14–2.80] in 2007 to 2011, and 2.69 [95% CI, 2.33–3.10] in 2012 to 2016). The HRs of chronic dialysis were 2.93 (95% CI, 2.40–3.58) in 2002 to 2006, 2.86 (95% CI, 2.32–3.52) in 2007 to 2011, and 3.30 (95% CI, 2.69–4.06) in 2012 to 2016 (Figure 4). Despite fluctuations, no statistically significant differences in the IRs of both acute and chronic dialysis across the 3 time periods were observed (P=0.06 and P=0.72, respectively). However, when differentiating diabetes, the IR of acute dialysis increased significantly across the 3 time periods among patients with diabetes (P=0.01) but decreased nonsignificantly for patients without diabetes (P=0.08). There were no significant differences observed in the IR of chronic dialysis over the time periods when stratified by diabetes (P=0.92 for patients with diabetes and P=0.93 for patients without diabetes). Following adjustments in the Cox regression model, we did find a significant interaction between the 3 different time periods and diabetes on the rates of acute dialysis (P=0.03) (Figure 4).

Temporal Trends in the IR and HR of Hospitalization Due to HF

A total of 26 184 patients (22.7%) were hospitalized at least once due to HF during a median follow-up of 2.3 years (IQR, 0.4–5 years]. Stratified by diabetes, 6224 patients (27.7%) with diabetes (median follow-up of 1.81 [IQR, 0.31–4.44]) and 19 960 patients (21.5%) without diabetes (median follow-up of 2.39 [IQR, 0.46–5.00]) were hospitalized due to HF. The IR of hospitalization for HF was 90.2 per 1000 person-years. The IRR comparing hospitalization due to HF (IR, 90.2 per 1000 person-years) and acute dialysis (IR, 8.0 per 1000 person-years) was 11.3, while hospitalization due to HF compared with chronic dialysis (IR, 3.5 per 1000 person-years) was 26.0. This indicates that patients with HF were more prone to be hospitalized due to HF than to initiating either type of dialysis. Among the patients with diabetes, the IRs of hospitalization for HF were 124.1, 116.4, and 129.5 per 1000 person-years in 2002 to 2006, 2007 to 2011, and 2012 to 2016, respectively, and 84.4, 80.6, and 85.1 per 1000 person-years for patients without diabetes (Figure 3A and 3B). After adjustments, the HRs of hospitalization for HF were significantly higher for patients with HF with

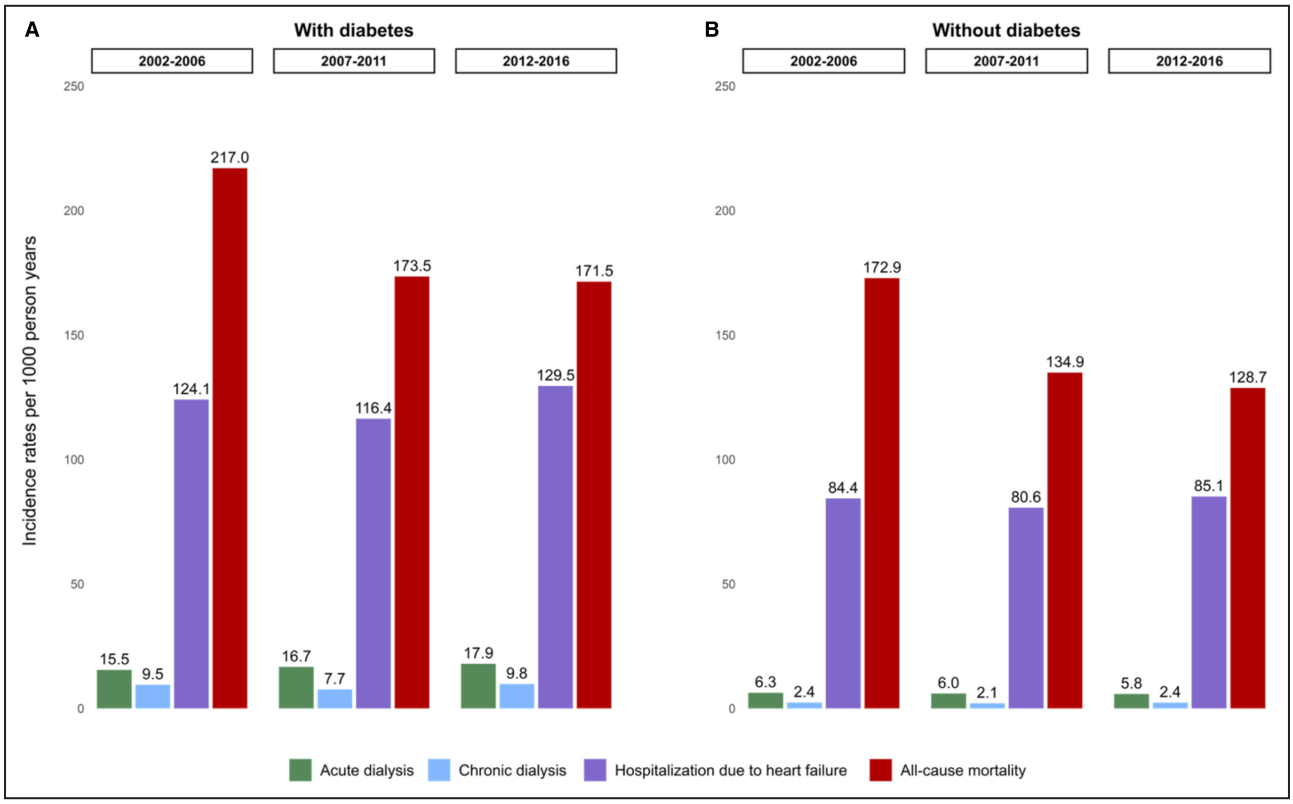

Figure 3. Incidence rates (IRs) of acute dialysis, chronic dialysis, hospitalization due to heart failure (HF), and all-cause mortality.

Five-year IRs per 1000 person-years according to the time periods 2002 to 2006, 2007 to 2011, and 2012 to 2016 stratified by status of diabetes at baseline. The plot portrays the 5-year IRs per 1000 person-years of acute dialysis, chronic dialysis, hospitalization due to HF, and all-cause mortality according to the time periods 2002 to 2006, 2007 to 2011, and 2012 to 2016 stratified by status of diabetes at baseline. **A** depicts the IR among patients with diabetes, and **B** depicts the IR amongs those without diabetes.

diabetes compared with patients without diabetes (HRs for patients with diabetes, where patients without diabetes constitute the reference group, 1.39 [95% CI, 1.32–1.46] in 2002–2006, 1.36 [95% CI, 1.29–1.43] in 2007–2011 and 1.40 [95% CI, 1.33–1.47] in 2012–2016) (Figure 4). The IRs of hospitalization for HF were generally stable, with no statistically significant change over time regardless of diabetes at baseline (P=0.72 overall; P=0.92 for patients with diabetes and P=0.93 for patients without diabetes).

Temporal Trends in the IR and HR of All-Cause Mortality

Within a median follow-up of 3.3 years (IQR, 1.2–5 years), 53 187 patients (46.0%) died from any cause, hereof 11 695 patients (52.0%) died in the group with diabetes (median follow-up of 2.80 [IQR, 1.02–5.00]), while 41 492 patients (44.6%) without diabetes died (median follow-up of 3.04 [IQR, 1.22–5.00]). The IR of all-cause mortality was 153.8 per 1000 person-years. The IRR for all-cause mortality compared with acute and chronic dialysis were 19.3 and 44.3, respectively, highlighting a substantial increase in the likelihood of mortality among patients with HF rather than initiating either type of dialysis. Among patients with diabetes, the IRs were 217.0, 173.5, and 171.5 per 1000 person-years in 2002 to 2006, 2007 to 2011, and 2012 to 2016, respectively, and 172.9, 134.9, and 128.7 per 1000 person-years for patients without diabetes (Figure 3A and 3B). Regardless of the time period at HF diagnosis, the mortality rates were significantly higher for patients with diabetes compared with patients without diabetes in both the unadjusted (Figure 3A and 3B) and adjusted (Figure 4) analyses. In contrast to the findings for acute dialysis, no significant interaction between the 3 different time periods and diabetes on the rates of chronic dialysis, hospitalization due to HF, and all-cause mortality were found (P>0.05 for all) (Figure 4). The overall mortality rate decreased numerically over time for both patients with diabetes (P=0.31) and those without diabetes (P=0.25) but did not reach statistical significance (Figure 3A and 3B).

Supplementary Analyses

The 5-year risk of the primary outcomes acute dialysis, chronic dialysis, hospitalization due to HF, and all-cause

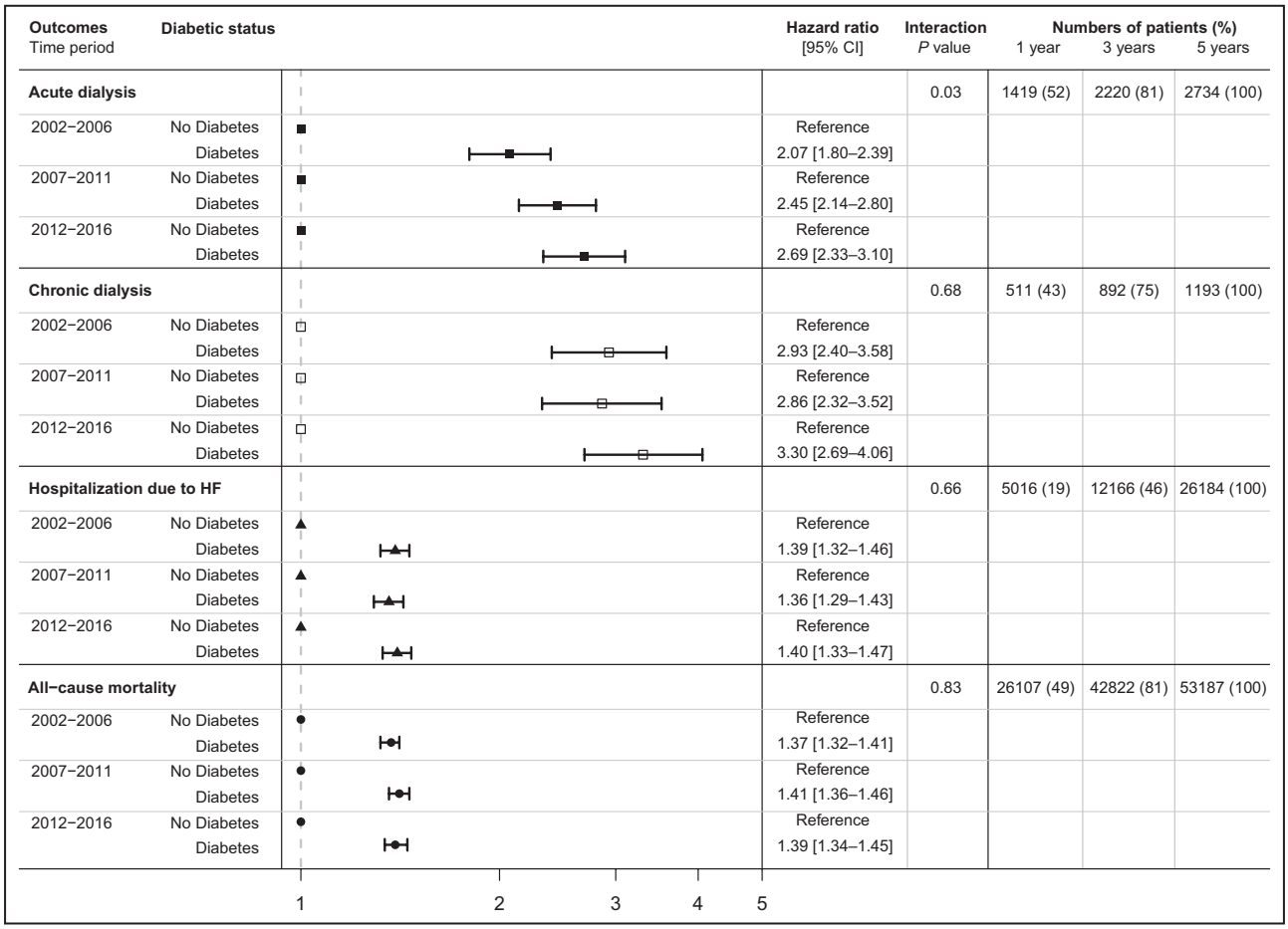

Figure 4. Adjusted hazard ratios (HRs) of acute dialysis, chronic dialysis, hospitalization due to heart failure (HF), and all-cause mortality for patients with HF with diabetes vs without diabetes according to time periods.
The forest plot illustrates the HR of acute dialysis, chronic dialysis, hospitalization due to HF, and all-cause mortality, respectively, for patients with diabetes vs without diabetes (without diabetes being the reference group). The *P* value for interactions indicates whether there was an interaction between being comorbid with diabetes and time periods for the 4 outcomes. The number and percentage of patients developing the outcomes at 1 year, 3 years, and 5 years after HF diagnosis, respectively, are presented. HRs were adjusted for age, sex, and history of comorbidity at baseline (hypertension, ischemic stroke, ischemic heart disease, atrial fibrillation).

mortality, according to diabetes status, stratified by age, are presented in Figures S1A through S1D, S2A through S2D, S3A through S3D, and S4A through S4D, respectively. Patients younger than 74 years had a higher absolute risk of acute and chronic dialysis compared with patients 74 years or older regardless of diabetic status. The 5-year risk of hospitalization due to HF was nearly equivalent for patients younger and older than 74 years. Patients 74 years or older had a nearly 2-fold risk of mortality compared with patients younger than 74 years.

In our sensitivity analysis presented in Figure S5A and S5B, we likewise included patients with HF and investigated the IR of long-term and short-term dialysis. Notably, our findings remained consistent with those observed in the context of acute and chronic dialysis. This consistency holds significance both in relation to the traditional HF end points as well as the impact of diabetes on the risk of developing the need for dialysis.

Figure S6 illustrates the subdistribution HRs of the outcomes generated by the Fine-Gray model, which closely aligns with the HRs derived from the Cox regression model, as depicted in Figure 4. This finding emphasizes the consistency and robustness of our findings regardless of the analytical approach.

The 1-year risk of mortality following incident initiation of acute dialysis, chronic dialysis, and hospitalization due to HF stratified by diabetes are presented in Figures S7A and S7B, S8A and S8B, and S9A and S9B, respectively. Patients receiving acute dialysis had a poorer prognosis compared with patients receiving chronic dialysis. In general, patients without diabetes exhibited significantly increased 1-year mortality risk following receiving either acute or chronic dialysis when compared with those with diabetes. However, diabetes was associated with significantly higher mortality risk following hospitalization due to HF.

DISCUSSION

Main Findings

This nationwide study demonstrated that acute and chronic dialysis were rare outcomes in patients with HF compared with traditional end points such as hospitalization due to HF and all-cause mortality. We found that over time the IR of acute dialysis increased significantly among patients with HF with diabetes, but decreased among individuals without diabetes. Moreover, our investigation revealed that the IR of chronic dialysis and hospitalization due to HF exhibited no significant temporal fluctuations. However, a noteworthy reduction in all-cause mortality rates was discerned over the same period. Furthermore, prevalent diabetes at the time of HF diagnosis was associated with higher rates of all outcomes, regardless of the time of HF diagnosis.

Temporal Trends in the Incidence of Acute and Chronic Dialysis

The IR of chronic dialysis was consistently low, which aligns with a previous cohort study conducted by Bosselmann et al in 2013 based on Danish HF clinic data (outpatients with HF with reduced ejection fraction referred for uptiration, patient education, and exercise training). A low incidence of dialysis (defined as the need for long-term dialysis ≥90 days) among patients with HF, with only 41 of 8204 patients (0.50%) receiving dialysis (IR of 1.3 of 1000 patient-years) during a 7-year follow-up period.[24] These findings led to the conclusion that the risk of dialysis was significantly less common compared with the risk of mortality. However, the observed disparity in the IR of dialysis between Bosselmann et al's study and our current study (IR of 3.5 of 1000 for chronic dialysis) might be attributed to differences in patient selection criteria. The present study included both inpatients and outpatients, with no exclusion based on reduced versus preserved ejection fraction. In major clinical trials involving patients with HF, the risk of composite renal end points has been evaluated.[4–6,25,26] The IR of dialysis observed in our study (8.0 of 1000 person-years for acute dialysis and 3.5 of 1000 person-years for chronic dialysis) is lower compared with the IR of the composite renal end point reported in these trials. For instance, in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and Reduced Ejection Fraction)[5] and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and Preserved Ejection Fraction),[6] the IRs were 16.0 per 1000 and 21.0 per 1000 person-years, respectively, in the treated groups compared with 31.0 per 1000 and 22.0 per 1000 person-years in the placebo groups. Similarly, in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, the IR was 8.0 per 1000 person-years in the treated group versus 12.0 per 1000 person-years in the placebo group.[4] The higher IR observed in these clinical trials can primarily be attributed to their utilization of a composite renal end point, which differs in definition among the trials, encompassing criteria such as chronic dialysis, renal transplantation, reduction or sustained estimated glomerular filtration rate (eGFR) <15 mL/min per 1.73 m^2, and renal death. Moreover, patients enrolled in these trials underwent careful selection based on specific inclusion and exclusion criteria encompassing symptoms, N-terminal pro-B-type natriuretic peptide, comorbidities, the expectation of good adherence, and medication. This careful selection process may have introduced patient selection, thereby contributing to the observed higher IRs. This underscores the importance of real-world data, without selection bias at enrollment, to obtain a more comprehensive understanding of the utilization and outcomes in patients with HF. Nonetheless, when comparing the IR of the renal end point to hospitalization for HF and all-cause mortality, similar trends in the proportion of the renal end point compared with hospitalization for HF and mortality were evident in both trials and our study. Several explanations may account for the low incidence of dialysis among patients with HF. First, there is a high competing risk of death that diverts patients away from reaching the renal end point of dialysis. Renal insufficiency in HF is closely associated with survival, indicating that those who survive are more likely to have better renal function, resulting in a reduced risk of requiring dialysis. Moreover, a subset of patients with HF with severe renal insufficiency may be considered too frail and deemed to be in a terminal stage, thus not benefiting from or being offered dialysis treatment, dependent on the clinician's assessment. These suggestions find support in the supplementary analysis, presenting an increased risk of acute and chronic dialysis among younger patients (younger than 74 years). This finding is consistent with previous studies that similarly found that higher age predicted a lower risk of end-stage kidney disease.[27–29] While HF and advanced age are not contraindications for receiving dialysis, our data suggest that patients with HF are not disadvantaged in terms of dialysis treatment. Especially, when comparing our data on patients with HF with other patient groups, such as those with diabetes alone, the former group appears to have a heightened risk for requiring dialysis.[12,13] This observation is consistent with the standards for timely dialysis access pathway establishment that are upheld in Denmark, as well as in the United States, serving as indicators of treatment quality. The clinical approach in Denmark closely aligns with KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, which emphasize the importance of selecting the correct modality and advocating

for establishing dialysis access during chronic kidney disease stages 4 and 5.[30] This typically corresponds to an eGFR of ±20 mL/min, contingent on the rate of progression. In 2021, a notable 69% (95% CI, 65%–73%) of patients with chronic kidney disease initiated dialysis as a planned procedure rather than as an emergency dialysis start due to end-stage kidney disease.[31]

Over the 3 time periods, we did observe fluctuations in the IR of both acute and chronic dialysis. The IR of acute dialysis among patients with diabetes increased significantly over the years, however, the IR decreased among patients without diabetes. Despite the improved life expectancy, increased prevalence of comorbidities, and enhanced survival among patients with HF, our study did not demonstrate a significant increase in the overall need for dialysis. This absence can be attributed to various factors, including the introduction of pharmacotherapy in HF treatment with nephroprotective properties; advancements in nonpharmacological interventions, such as cardiac resynchronization therapy and implantable devices; and implementation of multidisciplinary HF management programs, including close monitoring of fluid balance, optimization of medication regimens, dietary modifications, and patient education. These actions as well as the evolving interdisciplinary approach between cardiologists and nephrologists have probably led to earlier detection and monitoring of renal dysfunction resulting in prevention and delay of renal deterioration requiring dialysis. However, with a significant increase in the IR of acute dialysis among patients with HF with diabetes, there is a need for a heightened focus on this particular patient group. Furthermore, we observed that chronic dialysis was less frequently initiated by patients with HF compared with acute dialysis. This finding highlights a potential underutilization of chronic dialysis in patients with HF, suggesting the need for further investigation into the barriers and factors influencing the decision-making process surrounding the initiation of chronic dialysis in this patient population. Understanding and addressing these factors may help optimize the management and outcomes of patients with HF who could benefit from long-term dialysis treatment.

Relationship Between Diabetes and Initiation of Dialysis

The strong association between the diseases HF, diabetes, and renal insufficiency is widely acknowledged and numerous previous studies have already highlighted various aspects of the bidirectional relationship between these diseases.[32–37] The present study reinforces this association by revealing that patients with diabetes face a more than 2-fold increased risk of initiation dialysis treatment and a higher risk of acute dialysis over time compared with patients with HF without diabetes, suggesting that these patients are treated more aggressively today. From one point of view, this observation may be explained by a better general health condition and improvement in the drug therapy of both diabetes and HF, leading the physician to initiate acute dialysis in patients during acute illness. Though, our findings do also emphasize the significance of diabetes in the progression toward dialysis initiation, hospitalization for HF, and overall mortality. Consequently, it is imperative that this patient group receive particular attention in the routine management of patients with HF, as well as in the design and implementation of future clinical trials.

Methodological Considerations

Various methodological strengths apply to the present study. The primary strength of the study was the large and unselected sample size of a nationwide cohort, which enabled the inclusion of 115 533 Danish patients with incident HF. Additional strengths of the study were the completeness of data in the study population along with minimal selection bias in a real-world setting, due to all Danish citizens being identified by a unique Civil Personal Registration number. Due to the origin of the data from administrative registries, the findings of this study should be interpreted in light of some limitations. A limitation of the study was the lack of information on certain clinical variables, which may have caused unmeasured confounding, whereby the findings should be interpreted in that context. Information on left ventricular ejection fraction and New York Heart Association classification were absent, which could have supplied information on the HF phenotype and the degree of symptoms, respectively. Furthermore, as blood samples were not available, measurements of creatinine for the calculation of eGFR as well as N-terminal pro-B-type natriuretic peptides were not included in this study. Information on the staging of chronic kidney disease remains unaddressed in Danish registers, due to incomplete data concerning eGFR. Future studies could greatly benefit from including eGFR data, as this would enable the examination of patterns and potentially aid in the prevention of renal insufficiency. In addition, as our study derives its data from registries, the accuracy relies on health care professionals' diligent record-keeping. As mentioned in the Methodology section, we excluded 1489 patients who had received chronic dialysis prior to their HF diagnosis, but uncertainty remains regarding whether some of these patients initiated dialysis due to HF or volume overload, potentially indicating preexisting HF without an official diagnosis. Including these patients, the IR of dialysis observed in the present study would likely have been higher. Finally, the low incidence of dialysis should be viewed in the

context of a high level of attention to avoiding renal insufficiency during treatment with renin-angiotensin system inhibitors, angiotensin receptor neprilysin inhibitors, and mineralocorticoid receptor antagonists. This focus can and should not be changed based on our analyses.

CONCLUSIONS

In this nationwide study of patients with incident HF, we showed that the IRs of acute and chronic dialysis initiation were relatively low, with no significant change over time from 2002 to 2016. However, when stratified by diabetes, the IR of acute dialysis increased significantly among patients with diabetes. Despite decreasing mortality rates and constant rates of hospitalization for HF over time, dialysis remained a minor challenge in comparison. However, acute dialysis was initiated more frequently compared with the initiation of chronic dialysis. In addition, we found that diabetes was associated with significantly increased rates of acute and chronic dialysis, hospitalization due to HF, and all-cause mortality throughout all time periods. These findings may provide valuable information for future risk classification of patients with HF with or without diabetes and in the design of future clinical trials and selection of end points.

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S10

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