Clinical features, management and mortality in diabetic and non-diabetic patients with heart failure – observations from the COMMIT-HF registry

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Abstract

Introduction: Diabetes mellitus (DM) and heart failure (HF) are two common diseases that often co-exist.

Aim: To explore clinical characteristics, management strategies and rates of 3-year mortality among diabetic and non-diabetic patients hospitalised in a highly specialized interventional cardiology centre.

Material and methods: We used data from COMMIT-HF (COnteMporary Modalities In Treatment of Heart Failure), which is a single-centre, observational, prospective registry of patients with symptomatic chronic systolic HF (LVEF < 35%). Data collected included demographics, clinical characteristics, medical history, inpatient therapies and procedures. Follow-up was based on the information acquired from the national healthcare provider.

Results: We analysed 1397 patients out of the total of 1798 patients included in the COMMIT-HF registry between 2009 and 2013. We identified 595 (42.6%) diabetic and 802 (57.4%) non-diabetic patients. Compared to patients without DM, patients with type 2 DM had a higher rate of comorbidity. Frequency of death in patients with DM during the 3-year follow-up was significantly higher than in patients without DM (199 (33.4%) vs. 163 (20.3%), $p < 0.0001$, respectively).

Conclusions: In the analysed HF population representing patients receiving typical, everyday clinical care, the prevalence of DM is 42.6%. Diabetes mellitus has deleterious effects on renal function and symptoms as assessed by the New York Heart Association functional class. DM remains associated with increased frequency of death in patients with HF, in spite of recent pharmacological and device-based advances in HF management.

Key words: heart failure, diabetes mellitus, registry.

Streszczenie

Wstęp: Cukrzyca (DM) i niewydolność serca (NS) często ze sobą współistnieją.

Cel: Określenie charakterystyki klinicznej, postępowania i częstości występowania zgonów w ciągu 3 lat obserwacji u chorych z niewydolnością serca i współistniejącą cukrzycą oraz bez cukrzycy, którzy byli hospitalizowani w wysokospecjalistycznym ośrodku kardiologii interwencyjnej.

Materiał i metody: Do analizy włączono chorych z jednoośrodkowego, prospektywnego rejestru COMMIT-HF obejmującego chorych z objawową przewlekłą skurczową NS (LVEF < 35%). Analizowano dane demograficzne i kliniczne, przebieg choroby, stosowane leczenie oraz zabiegi. Dane dotyczące rokowania odległego uzyskiwano z Narodowego Funduszu Zdrowia.

Wyniki: Retrospektywnej analizie poddano dane 1397 kolejnych chorych spośród 1798 osób włączonych do rejestru COMMIT-HF w latach 2009–2013 w specjalistycznym ośrodku kardiologii interwencyjnej. W badanej grupie było 595 (42,6%) chorych z cukrzycą i 802 (57,4%) bez towarzyszącej cukrzycy. U chorych z cukrzycą występowało istotnie więcej schorzeń współistniejących niż u chorych bez cukrzycy. Częstość występowania zgonów podczas 3 lat obserwacji była wyższa u chorych z cukrzycą niż bez cukrzycy (199 (33,4%) vs 163 (20,3%), $p < 0,0001$).

Wnioski: W badanej grupie chorych z NS z codziennej praktyki klinicznej odsetek osób z cukrzycą wynosił 42,6%. Cukrzyca wpływała niekorzystnie na funkcję nerek oraz zaawansowanie NS oceniane wg klasyfikacji NYHA. Mimo postępów w leczeniu farmakologicznym i interwencyjnym NS cukrzyca była związana ze zwiększoną częstością występowania zgonów.

Słowa kluczowe: niewydolność serca, cukrzyca, rejestr.

Introduction

Diabetes mellitus and heart failure (HF) are two common diseases that often co-exist. The prevalence of diabetes mellitus among patients with HF is high, and it has been estimated as between 30% and 50% [1, 2]. The Framingham Heart Study demonstrated that the risk of HF in diabetes is increased 2.4-fold in men and fivefold in women compared to the non-diabetic population [3]. Diabetes mellitus affects the heart in three ways: cardiac autonomic neuropathy, coronary artery disease due to accelerated atherosclerosis, and diabetic cardiomyopathy (DCM) [4]. Moreover, the HF complicates the treatment of diabetes mellitus by altering the pharmacokinetics of anti-diabetic medications. Thus, early detection and management of these patients is important, especially considering the worse prognosis of HF in diabetic patients. In order to improve the prognosis of patients with dangerous intersection of HF and diabetes it is necessary to optimise the treatment of both disorders. The observational registries and randomised clinical trials that have explored the prognostic impact of diabetes on survival outcomes in patients with HF have reported inconclusive or conflicting results [5–12].

Aim

The aim of the study was to explore clinical characteristics, management strategies and rates of 3-year mortality among diabetic and non-diabetic patients hospitalised in a highly specialised interventional cardiology centre.

Material and methods

We used data from COMMIT-HF (COnteMporary Modalities In Treatment of Heart Failure), which is a single-centre, observational, prospective registry previously described [13]. Briefly, between January 2009 and December 2013, 1798 patients with symptomatic chronic systolic HF (LVEF < 35%) hospitalised in a highly specialised cardiology centre were included in COMMIT-HF. There were no specific exclusion criteria for patients included in the registry, except for age < 18 years and acute coronary syndrome as a reason for index hospitalisation. Data collected included demographics, clinical characteristics, medical history, in-patient therapies and procedures. Three-year follow-up of survival was based on the information acquired from the national health-care provider. The current manuscript reports a sub-analysis of the COMMIT-HF registry focusing on the impact of diabetes on the clinical features, treatment and long-term outcomes. After excluding patients with type 1 diabetes ($n = 9$), impaired glucose tolerance ($n = 191$) as well as incomplete clinical and laboratory data ($n = 201$), there were 1397 patients in our final analysis. Heart failure was diagnosed by the attending physician based on guideline recommendations at the time of inclusion. New York Heart Association (NYHA) functional classes I to IV were used to define HF severity. Ischaemic aetiology of HF was diagnosed in case of a confirmed coronary revascularisation procedure or a history of previous myocardial infarction. In patients with an unknown aetiology

of HF, coronary angiography was performed. A diagnosis of diabetes mellitus was made when one of the following criteria was met: 1. a diagnosis of diabetes mellitus was previously established and documented in the patient's medical records 2. the patient had a current prescription for oral hypoglycaemic medication or insulin. Comorbidities were defined as the presence of any or several of the following: anaemia, chronic kidney disease, obesity, arterial hypertension, atrial fibrillation and peripheral vascular disease. Estimated glomerular filtration rate (eGFR) was calculated with the MDRD formula, and an eGFR < 60 ml/min/1.73 m^2 was considered the cut-off for chronic kidney disease. The registry and this study conform to the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using SAS software, version 9.4 (SAS Institute Inc, Gary, NC). Continuous variables were expressed as mean ± standard deviation (SD), if normally distributed, or as median (25th–75th percentile), if skewed. Categorical data were summarised as frequencies and percentages. Characteristics of patients categorised by diabetes status were compared by Student's t-test, the Mann-Whitney test or the χ^2 test, as appropriate. The Kaplan-Meier method with log-rank testing was used to compare survival probability between diabetes and non-diabetes groups. The interpretation of statistical significance was based on a p-value of less than 0.05.

Results

We analysed 1397 patients out of the total of 1798 patients included in the COMMIT-HF registry between 2009 and 2013. We identified 595 (42.6%) diabetic and 802 (57.4%) non-diabetic patients. Compared to patients without diabetes, patients with type 2 diabetes were older, more often had ischaemic aetiology of heart failure and had a higher comorbidity rate. Diabetics did not differ from non-diabetics in terms of echocardiographic parameters (Tab. I).

Table II shows the baseline laboratory characteristics of the included 1397 patients, according to the presence or absence of diabetes mellitus.

Table III shows baseline pharmacotherapy according to the presence or absence of diabetes mellitus. In the patients with diabetes mellitus the most commonly prescribed treatments were insulin, followed by sulfonylureas, and biguanides (Tab. IV).

Figure 1 shows cumulative probability of all-cause mortality among diabetic and non-diabetic patients. Frequency of death in patients with diabetes during the 3-year follow-up was significantly higher than in patients without diabetes (199 (33.4%) vs. 163 (20.3%), $p < 0.0001$, respectively).

Discussion

There are some findings of major importance in this study of a large HF population representing patients re-

Tab. I. Baseline patient characteristics

Parameter	Non-diabetics N = 802 (57.4%)	Diabetic N = 595 (42.6%)	*P*-value
Age [years]	59.8 (51.3–68.7)	63.2 (55.9–72.3)	< 0.001
Male (%)	644 (80.4)	467 (78.5)	NS
Anaemia (%)	263 (32.8)	227 (38.2)	< 0.05
Chronic kidney disease (%)	186 (23.2)	215 (36.1)	< 0.001
NYHA I (%)	125 (15.6)	58 (9.7)	< 0.001
NYHA II (%)	258 (32.2)	170 (28.6)	< 0.001
NYHA III (%)	335 (41.8)	277 (46.6)	< 0.001
NYHA IV (%)	83 (10.4)	90 (15.1)	< 0.001
Ischaemic aetiology (%)	480 (60)	405 (68)	< 0.01
ICD/CRT-D (%)	565 (70.5)	385 (64.7)	< 0.05
Arterial hypertension (%)	367 (46)	382 (64.4)	< 0.001
Atrial fibrillation (%)	202 (25.3)	184 (31)	< 0.05
Peripheral vascular disease (%)	30 (3.8)	37 (6.2)	< 0.05
Obesity (%)	87 (10.9)	173 (29.2)	< 0.001
LVDD [mm]	64.0 (58.0–71.0)	63.0 (58.0–70.0)	NS
RV [mm]	31.0 (27.0–34.0)	30.0 (27.0–34.0)	NS
LA [mm]	45.0 (40.0–50.0)	45.0 (41.0–50.0)	NS
LVEF (%)	26.0 (22.0–30.0)	27.0 (22.0–31.0)	NS

NYHA – New York Heart Association, ICD/CRT-D – implantable cardioverter-defibrillator/cardiac resynchronisation therapy, LVDD – left ventricular diastolic diameter, RV – right ventricle, LA – left atrium, LVEF – left ventricular ejection fraction

Tab. II. Baseline laboratory characteristics

Parameter	Non-diabetics (N = 802)	Diabetics (N = 595)	*P*-value
Haemoglobin [mmol/l]	8.7 (8.0–9.4)	8.6 (7.8–9.3)	< 0.05
AST [U/l]	25.6 (20.0–35.3)	25.4 (19.9–36.0)	NS
ALP [U/l]	25.0 (17.5–40.1)	26.00 (17.9–41.0)	NS
Bilirubin [μmol/l]	12.6 (8.7–19.1)	12.8 (8.9–20.1)	NS
Creatinine [μmol/l]	87.0 (72.8–107.0)	93.2 (79.0–121.0)	< 0.001
Uric acid [μmol/l]	409.2 (332.0–496.9)	432.8 (349.6–537.0)	< 0.05
HbA$_{1c}$ (%)	5.9 (5.6–6.0)	6.7 (6.2–7.3)	< 0.001
Sodium [mmol/l]	137.3 (135.0–139.0)	137.2 (134.9–139.0)	NS
Platelets [10^3/mm^3]	194.0 (161.0–238.0)	207.5 (169.0–249.0)	< 0.001
NT-proBNP [pg/ml]	890.0 (547.0–3275.0)	1403.0 (654.0–3704.0)	< 0.05

AST – aspartate aminotransferase, ALP – alkaline phosphatase, HbA$_{1c}$ – glycated haemoglobin, NT-proBNP – N-terminal pro-B-type natriuretic peptide

ceiving typical, everyday clinical care. Our analysis has shown that patients with HF and type 2 diabetes mellitus have significantly higher frequency of all-cause mortality during the 3-year follow-up than similar patients without diabetes, in spite of widespread administration of β-blockers and guideline-based application of angiotensin-converting-enzyme inhibitors, aldosterone receptor antagonists and device-based therapy. In our study we also examined the characteristics of patients with HF and diabetes mellitus and demonstrated that diabetes has deleterious effects on renal function, haemoglobin and symptoms as assessed by the New York Heart Association functional class. Moreover, we found that the frequency of obesity was significantly higher in diabetic than in non-diabetic patients.

Our study showed that HF was not managed differently in the field of basic HF medications such as β-blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, aldosterone receptor antagonists or digitalis in patients with and without diabetes mellitus. A larger proportion of patients with diabetes mellitus was on diuretics, but in this group there was a larger proportion of advanced HF patients. More extensive use of statins in diabetic patients in our study is not clear. Statins did not prove to be beneficial in HF patients when prescribed in the absence of other indications [14]. We observed higher rates of

antiplatelet drugs in diabetic patients, probably because of a larger proportion of ischemic aetiology of HF in this group.

Our data support prior studies that have also found an association between diabetes mellitus and increased risk of all-cause mortality in HF [5–9]. Despite these data, the association between diabetes mellitus and HF remains under-recognised by clinicians [15]. Nonetheless, in an era in which there is increasing emphasis on chronic disease management as a strategy to contain healthcare costs, these findings highlight the significance of diabetes mellitus and the need for therapies that improve outcomes in this population. Multiple hypotheses have been proposed for the mechanism behind the association of diabetes mellitus and HF, including medical comorbidities associated with diabetes mellitus, medications used in the treatment of diabetes mellitus, and a direct metabolic effect of altered glucose regulation, but the exact mechanism remains poorly defined [16]. A subgroup analysis of the SOLVD (Studies of Left Ventricular Dysfunction) treatment trial suggested that diabetes was an independent predictor of all-cause mortality in chronic HF patients with reduced ejection fraction and ischaemic aetiology [10]. Data from patients with reduced and preserved left ventricular ejection fraction recruited to the CHARM (Candesartan in Heart Failure) program supported our conclusion that diabetes has an impact on prognosis in HF [6]. This is in spite of our different study design (registry versus randomised trial), inclusion criteria and management strategies. Cubbon *et al.* found that patients with HF and type 2 diabetes have a risk of all-cause mortality double that of similar patients without diabetes [8]. In accordance with our study, in the Swedish Heart Failure Registry type 2 diabetes mellitus was associated with higher all-cause mortality [11]. In addition, the vast majority of diabetic patients with HF from the above registry had one or more manageable comorbidities. Moreover, the multicenter observational prospective cohort EPI-CAL STUDY which has included 499 hospitalised HF patients has shown that one of the prognostic factors of death during long-term follow-up was diabetes mellitus. Our results are in conflict with results of the Norwegian Heart Failure registry, which did not show an association between diabetes mellitus and mortality [12]. The Norwegian Heart Failure Registry differed from our study because it was a cohort of a real life population treated at outpatient HF clinics. In the above study compared to our analysis, patients were older, diabetic patients were on higher doses of diuretics and β-blockers, and a larger proportion of them were treated with aldosterone receptor antagonists and statins compared to non-diabetic patients. Moreover, Di Angelantonio *et al.* in a meta-analysis of observational studies observed similar mortality risk for diabetic subjects and patients who had experienced a stroke previously [17]. Analysis of the multicenter REACT REGISTRY which was conducted between 2010 and 2013 in Brazil showed that diabetes was not a cardiovascular risk equivalent [18].

The major strength of the present report is the size and unselected nature of the population, which reflects con-

Tab. III. Baseline pharmacotherapy

Parameter	Non-diabetics (*N* = 802)	Diabetics (*N* = 595)	*P*-value
β-blockers (%)	770 (96.1)	571 (96.0)	NS
ACE inhibitors (%)	735 (91.5)	549 (92.2)	NS
ARBs (%)	67 (8.5)	46 (7.8)	NS
Diuretics (%)	640 (80.6)	511 (86.5)	< 0.05
Spironolactone (%)	556 (70)	434 (73.4)	NS
Eplerenone (%)	105 (13.2)	80 (13.5)	NS
Statin (%)	579 (73.4)	461 (78.1)	< 0.05
Digitalis (%)	175 (22.2)	156 (26.4)	NS
Allopurinol (%)	206 (26.2)	208 (35.3)	< 0.05
Antiplatelet drug (%)	541 (67.1)	447 (75.5)	< 0.05
Anticoagulants (%)	256 (32.5)	205 (34.7)	NS
Amiodarone (%)	88 (11.2)	66 (11.2)	NS
Ivabradine (%)	29 (3.7)	73 (12.4)	< 0.001

ACE – angiotensin-converting enzyme, ARBs – angiotensin II receptor blockers

Tab. IV. Baseline antidiabetic treatment (*N* = 597)

Diet	65 (11%)
Metformin	52 (8.7%)
Sulfonylureas	211 (35.3%)
Insulin	269 (45%)
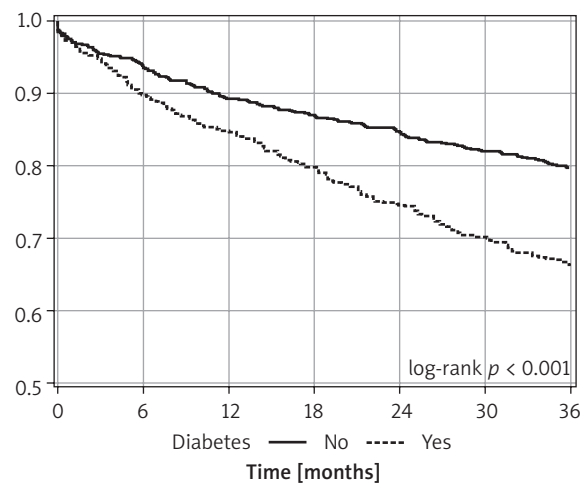
Fig. 1. Kaplan-Meier curve of cumulative frequency of death according to the presence or absence of diabetes mellitus

temporary, everyday clinical practice. One limitation with registry data is the possibility of varying diagnostic criteria. The registry defines the different variables, but they have not been validated in any detail. The proportion with diabetes mellitus is probably an underestimation, because undiagnosed diabetes is common in populations with cardiovascular diseases [19, 20]. As with most other registries, hospital enrolment was voluntary; thus our findings may not be representative of clinical practice in all hospitals of

the country. Additionally, the study results could have been affected by unmeasured confounding variables, such as socio-economic strata, patient preferences and post-hospital care. Information about duration of diabetes, the use of different classes of oral hypoglycaemic agents, and causes of mortality, as well as follow-up data on HbA_{1c} measurements, was not available.

Conclusions

Among patients hospitalised with heart failure the prevalence of diabetes mellitus is 42.6%. In diabetic patients co-morbidities are more frequent than in non-diabetics. Diabetes mellitus has deleterious effects on renal function and symptoms as assessed by the New York Heart Association functional class. Diabetes mellitus remains associated with increased frequency of death in patients with HF, in spite of recent pharmacological and device-based advances in HF management. The three-year survival of our population with diabetes and HF suggests that there is scope to dramatically improve overall HF outcomes if effective diabetes-specific HF management can be defined. Our findings indicate that nationwide primary prevention programmes are greatly needed, in addition to the establishment of HF programmes to improve patient compliance and outcomes.

Disclosure

Authors report no conflict of interest.

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