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# Does renal function influence the prognostic impact of type 2 diabetes mellitus in patients with chronic heart failure and left ventricular dysfunction?☆

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ABSTRACT

*Hypothesis:* Type 2 diabetes mellitus (T2DM) and chronic heart failure (CHF) are associated with renal dysfunction. We tested the hypothesis that the degree of renal dysfunction influences the negative impact on the outcome of T2DM in patients with CHF and reduced left ventricular ejection fraction (LVEF).
*Methods:* From November 1, 2009 to December 31, 2012, the "Trieste Registry of CV Diseases" enrolled 19,589 patients. Those with diagnosis of CHF and reduced LVEF were analyzed. The primary end-point was all-cause mortality.
*Results:* 554 patients were selected (73 ± 10 years old, 32% females), 192 had T2DM (35%). During follow-up (23 ± 11 months), all-cause death occurred in 57 patients (30%) who had T2DM and in 58 (16%, $p < 0.001$) who had not; T2DM was associated with an increased risk of death (adjusted HR 2.55 [95% CI 1.02-6.36], $p = 0.04$). The prognostic impact of T2DM was lost when patients were selected according to renal function: adjusted HR 1.44 [0.21-9.93], $p = 0.71$, in patients with normal renal function, defined as estimated glomerular filtration rate (eGFR) >60, and adjusted HR 3.37 [0.96-11.80], $p = 0.08$ in patients with renal dysfunction (eGFR < 60 ml/min * 1.73 $m^2$). T2DM predicted all-cause mortality only in the subgroup with eGFR between 90 and 30 ml/min * 1.73 $m^2$ (adjusted HR 2.52 [1.01-6.30], $p = 0.04$).
*Conclusions:* In patients with CHF and reduced LVEF the prognostic impact of T2DM depends on the degree of renal dysfunction. Its contribution in all-cause mortality risk prediction is limited to mild–moderate renal dysfunction subgroup, while prognostic power is lost in normal renal function and in severe renal dysfunction patients.


## 1. Introduction

Chronic heart failure (CHF) and chronic renal disease (CKD) often co-exist and their presence is due to the increasing age of the general population, the reduction of renal perfusion due to the impairment of systolic cardiac performance and the tailored treatment of both conditions [1]. These two syndromes have common predisposing factors such as hypertension, type 2 diabetes mellitus (T2DM), obesity and atherosclerosis, so that they share the same pathophysiological mechanisms of disease. The negative impact of CKD on clinical outcomes in patients with CHF is notorious [2–4], and in those patients in whom CKD coexists with T2DM, the mortality rate is particularly high, above the entire cardiovascular one [5]. Even T2DM is a well-recognized predictor of outcome in patients with CHF [4–8]. However, it is not clear whether its prognostic impact is influenced in some way or fully independent of the grade of CKD in these patients. As an example, we recently demonstrated that in patients with severe renal dysfunction

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hospitalized for an episode of acute heart failure, the presence of T2DM had a paradoxical protective effect on one-year all-cause mortality [9]. Accordingly, we analyzed a large cohort of patients with CHF with the aim of assessing whether the degree of CKD may influence the prognostic role of T2DM in these patients.

## 2. Methods

From November 1, 2009 to December 31, 2012, 19,589 patients who underwent cardiovascular (CV) ambulatory evaluation were included in the "Trieste Registry of CV Diseases". Clinical data were derived from the E-data chart for outpatient clinic (Cardionet®) of CV Center of Trieste, Italy, and collected in a regional Data Warehouse. Data on patients with a diagnosis of CHF and reduced left ventricular ejection fraction (LVEF, defined as values of LVEF < 50%) were analyzed. All patients gave their consent to this study and the anonymous management of their individual data. The study protocol was approved by the local institutional review boards. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki as revised in 2000.

CHF was defined according to the recent guidelines [10]. All patients underwent a complete echocardiogram where LVEF was calculated in a biplane mode according to the Simpson's methods. T2DM was primarily defined as a history of diabetes (self-report or retinopathy), use of medications to treat T2DM or newly diagnosed T2DM defined as fasting blood glucose of 126 mg/dl or non-fasting blood glucose of 200 mg/dl in the absence of self-report or medication use.

Renal function was expressed as estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI equation [11]. The study population was divided in 5 subgroups based on the K/DOQI classification: class I (normal eGFR) = eGFR $\geq$ 90; class II (mild CKD) = eGFR 60-89; class III (moderate CKD) = eGFR 30-59; class IV (severe CKD) = eGFR 15-29; class V (kidney failure) = eGFR < 15 ml/min * 1.73 $m^2$) [12]. All clinical characteristics of these patients are summarized in Table 1.

**Table 1**
Main clinical characteristics of the 554 study patients with chronic heart failure and reduced left ventricular ejection fraction divided according to the presence of type II diabetes mellitus. Age is the age of patients at their first visit; Female gender (or female) is the percentage of patients of female sex; Body mass index is the ratio between weight and height squared; Obesity is the percentage of patients with body mass index > 30; History of Hypertension is the percentage of patients with hypertension in therapy.

| Variables | Yes Diabetes (192 patients) | No Diabetes (362 patients) | *p* | Total study population (554 patients) |
|---|---|---|---|---|
| Clinical | | | | |
| *Age* (years) | *72 ± 9* | *74 ± 10* | *0.03* | *73 ± 10* |
| *Female gender* (%) | *24* | *35* | *0.009* | *32* |
| *Body mass index* (kg/$m^2$) | *27.1 ± 5.2* | *25.9 ± 4.0* | *0.004* | *26.3 ± 4.5* |
| *Obesity* (%) | *30* | *17* | *<0.001* | *21* |
| *History of hypertension* (%) | *82* | *67* | *<0.001* | *72* |
| NYHA functional class (1-4) | 2.3 ± 0.6 | 2.2 ± 0.6 | 0.34 | 2.2 ± 0.6 |
| NYHA class 3-4 (%) | 31 | 26 | 0.41 | 28 |
| Atrial fibrillation | 42 | 46 | 0.38 | 44 |
| Ischemic etiology of heart failure | 68 | 56 | 0.38 | 61 |
| Systolic blood pressure (mm Hg) | 131 ± 19 | 130 ± 20 | 0.70 | 130 ± 20 |
| Diastolic blood pressure (mm Hg) | 77 ± 9 | 76 ± 11 | 0.22 | 77 ± 11 |
| Heart rate (beats/min) | 74 ± 16 | 73 ± 18 | 0.64 | 73 ± 17 |
| Laboratory | | | | |
| Hemoglobin (gr/dl) | 13.2 ± 1.5 | 13.5 ± 1.7 | 0.16 | 13.4 ± 1.6 |
| *HbA1c* (%) | *7.2 ± 1.1* | *6.3 ± 1.2* | *0.02* | *7.0 ± 1.3* |
| Azotemia (mg/dl) | 56 ± 32 | 52 ± 30 | 0.16 | 53 ± 30 |
| GFR (ml/min/1.73 $m^2$) | 61 ± 25 | 64 ± 22 | 0.31 | 63 ± 23 |
| GFR (class 1-5) | 2.7 ± 1.2 | 2.5 ± 1.2 | 0.19 | 2.6 ± 1.2 |
| *GFR < 60* ml/min/1.73 $m^2$ (%) | *53* | *37* | *0.01* | *44* |
| Serum sodium (mEq/l) | 140 ± 3 | 140 ± 3 | 0.31 | 140 ± 3 |
| Serum potassium (mEq/l) | 2.5 ± 0.6 | 4.4 ± 0.5 | 0.32 | 4.4 ± 0.5 |
| Echocardiography | | | | |
| LV end-diastolic volume (ml/$m^2$) | 75 ± 27 | 77 ± 28 | 0.39 | 77 ± 27 |
| LV end-diastolic volume (ml/$m^2$) | 50 ± 22 | 51 ± 23 | 0.65 | 50 ± 23 |
| LV ejection fraction (%) | 35 ± 9 | 36 ± 9 | 0.29 | 36 ± 9 |
| LV wall motion score index (1–3) | 2.01 ± 0.42 | 2.01 ± 0.41 | 0.97 | 2.01 ± 0.42 |
| LV relative wall thickness | 0.38 ± 0.10 | 0.38 ± 0.11 | 0.47 | 0.38 ± 0.11 |
| LV mass (height$^2$) | 67 ± 20 | 70 ± 21 | 0.2 | 69 ± 21 |
| *E/E′* | *19.6 ± 10.9* | *16.8 ± 9.1* | *0.03* | *17.8 ± 9.8* |
| *Pulmonary capillary wedge pressure* (mm Hg) | *26 ± 11* | *23 ± 13* | *0.03* | *24 ± 12* |
| *Severe LV diastolic dysfunction* (%) | *59* | *46* | *0.04* | *50* |
| Moderate-severe mitral regurgitation (%) | 28 | 36 | 0.14 | 33 |
| Left atrial area ($cm^2$) | 29 ± 8 | 29 ± 8 | 0.59 | 29 ± 8 |
| *Pulmonary artery systolic pressure* (mm Hg) | *42 ± 14* | *38 ± 14* | *0.01* | *40 ± 14* |
| Pharmacological treatment | | | | |
| Betablockers (%) | 40 | 42 | 0.67 | 42 |
| ACEi/ARB (%) | 64 | 61 | 0.48 | 62 |
| Diuretics (%) | 42 | 46 | 0.27 | 44 |
| Aldosterone antagonist (%) | 32 | 26 | 0.11 | 28 |
| Digitalis (%) | 23 | 19 | 0.19 | 20 |
| Nitrates (%) | 37 | 32 | 0.31 | 34 |
| *Antiplatelets agents* (%) | *67* | *55* | *0.007* | *59* |
| Anticoagulant (%) | 16 | 21 | 0.14 | 19 |
| *Statins* (%) | *50* | *38* | *0.006* | *42* |