Julián *et al. Cardiovascular Diabetology* (2025) 24:104
https://doi.org/10.1186/s12933-025-02632-9

Cardiovascular Diabetology

RESEARCH Open Access

Long-term trajectory of estimated glomerular filtration rate in ambulatory patients with type 2 diabetes and heart failure: clinical insights and prognostic implications

Maria Teresa Julián[1†], Pau Codina[2,3,4†], Josep Lupón[2,3,4], Elisabet Zamora[2,3,4], Alejandra Pérez-Montes de Oca[1], Mar Domingo[2], Evelyn Santiago-Vacas[2], Andrea Borrellas[2], María Ruiz-Cueto[2], Carlos González-Gallego[1], Maribel Troya[5], Gregorio A. Romero-González[5], Nuria Alonso[1,3,6*] and Antoni Bayes-Genis[2,3,4*]

Abstract

Background Although previous studies have evaluated renal function decline in patients with heart failure (HF), there is limited evidence on long-term renal trajectories, especially in patients with concomitant HF and type 2 diabetes (T2D). This study aims to provide a detailed analysis of renal function decline over an extended follow-up period in a well-characterized cohort of patients with HF and T2D.

Methods This is a post hoc subanalysis of a prospective registry involving ambulatory patients with HF and T2D referred to a specialized HF clinic. The estimated glomerular filtration rate (eGFR) was assessed at baseline and during scheduled follow-up visits every three months using the Chronic Kidney Disease Epidemiology Collaboration formula. Loess curves were plotted for predefined subgroups, and multivariable longitudinal Cox regression analyses were performed to evaluate the associations between eGFR trajectories and all-cause mortality.

Results A total of 1,114 patients with HF and T2D were included, with a mean age of 69.3 ± 10.3 years, and 68.2% were men. In total, 10,830 scheduled creatinine measurements were analysed, with a mean of 15.8 ± 9.4 measurements per patient. A significant progressive decline in the eGFR was observed, with an average annual rate of − 2.05 (95% CI − 2.11 to − 1.95, $p < 0.001$) ml/min/1.73 m^2. Subgroup analysis indicated that older age, nonischaemic HF aetiology, HFpEF or HFmrEF, poor glycaemic control, and higher baseline eGFRs were associated with a more pronounced decline in renal function. Furthermore, a decrease in the eGFR was independently associated with an increased risk of all-cause mortality.

[†]Maria Teresa Julián and Pau Codina contributed equally to this work.

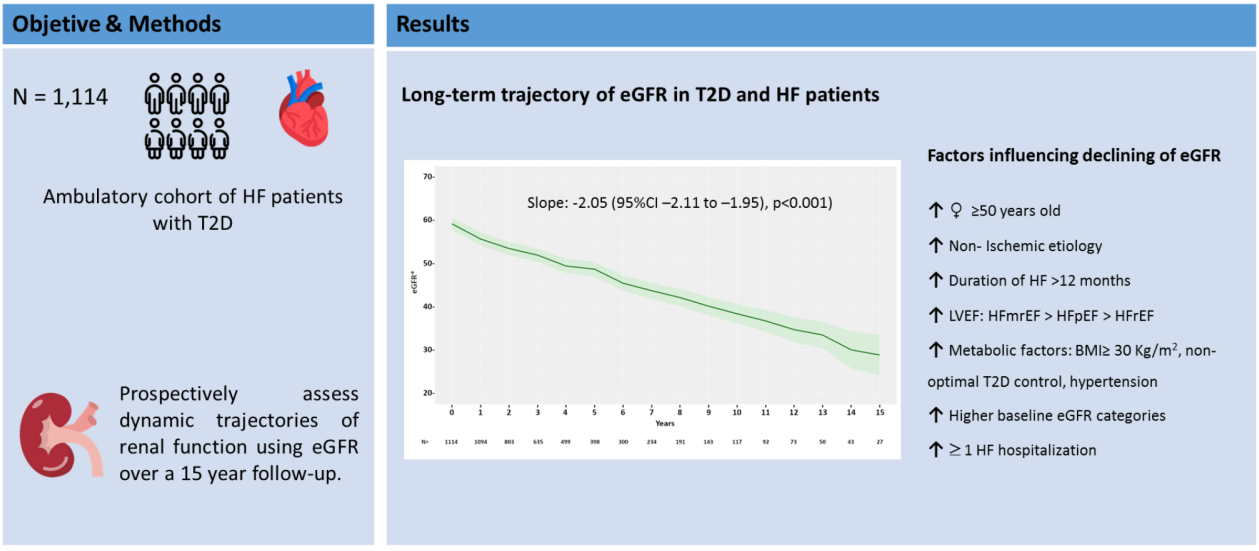
*Correspondence:
Nuria Alonso
nalonso32416@yahoo.es
Antoni Bayes-Genis
abayesgenis@gmail.com

Full list of author information is available at the end of the article

Conclusions This study offers novel insights into long-term renal function trajectories in patients with HF and T2D and identifies key clinical factors associated with accelerated renal decline. Future research is warranted to validate these results in larger, more diverse cohorts and to explore potential therapeutic interventions.

Keywords Heart failure, Diabetes mellitus, Estimated glomerular filtrate rate, Slope, Kidney function

Graphical Abstract



T2D: type 2 diabetes; HF:heart failure; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; HFmrEF: heart failure with mildly-reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; BMI: body mass index

Introduction

Epidemiological and clinical studies consistently emphasize a strong link among cardiovascular, renal and metabolic diseases, with type 2 diabetes (T2D) being a major underlying risk factor [1]. T2D is associated with a two-to-fourfold increased risk of atherosclerotic cardiovascular disease (CVD), including heart failure (HF) [2]. Conversely, patients with HF exhibit a higher prevalence of T2D (20%) compared to those without HF (4–6%) [3]. Additionally, diabetes is a major risk factor for the development of chronic kidney disease (CKD) [4]. Recent epidemiological studies indicate a CKD prevalence of approximately 40% among individuals with T2D [5] and 50% among those with HF [6]. Numerous studies have established a link between a decline in kidney function over time and the risk of kidney failure, as well as increased all-cause mortality and cardiovascular disease risk [7, 8]. As a result, the simultaneous occurrence of T2D, HF and CKD is common, with each condition worsening the prognosis of the others.

The bidirectional interplay between kidney disease and cardiac remodelling that leads to HF in the context of T2D is complex and multifactorial. Multiple mechanisms contribute to diabetes-associated cardiac and renal dysfunction, including impaired microvascular endothelial function, increased oxidative stress and inflammation, haemodynamic changes, gluco-lipotoxicity, and local activation of neurohormonal systems, including the renin–angiotensin and sympathetic nervous systems [1, 4]. In addition to hyperglycaemia, the coexistence of various cardiovascular risk factors, such as hypertension, obesity, and dyslipidaemia, can exacerbate cardiorenal complications in individuals with T2D.

A progressive decline in renal function, as assessed using the estimated glomerular filtration rate (eGFR), frequently occurs in patients with T2D, as well as in those with HF. Therefore, it is imperative to gain a more comprehensive understanding of the long-term patterns in kidney function and to pinpoint patients with HF who are at heightened risk of declining kidney function. This approach is crucial for optimizing the implementation of medical therapy per established guidelines. The recent emergence of several novel drug classes (such as angiotensin receptor/neprilysin inhibitor [ARNI] and sodium glucose cotransporter 2 inhibitors [iSGLT2]) and the 2021 ESC guidelines advocating for the early commencement and adjustment of disease-modifying treatments suggest the possibility of treatment-related alterations in renal function. This perceived risk might lead to reluctance in initiating and escalating these crucial therapies [9, 10].

In a recent study, we provided the first comprehensive analysis of eGFR dynamics in a real-world cohort of ambulatory patients with HF [11]. In that study, patients with T2D presented a more unfavourable eGFR trajectory compared to those without diabetes. To our knowledge, information on the pronounced long-term decline in kidney function among patients with T2D and underlying heart failure is limited. The objective of this study was to explore the extended-term (up to 15 years) trajectory of the eGFR in a well-characterized cohort of individuals with T2D and HF and to examine its association with mortality.

Methods

Study design and population

This study is a T2D-focused post hoc subanalysis of a previously reported cohort [11]. All consecutive ambulatory patients referred to a structured multidisciplinary HF clinic at a university hospital between August 2001 and December 2021, regardless of aetiology, were considered for the study. The inclusion criteria were patients diagnosed with T2D and HF with at least one HF hospitalization or reduced left ventricular function, according to the European Society of Cardiology Guidelines. Patients had to be ambulatory, attend regular follow-up in an HF clinic, and have at least 12 months of follow-up data, including two or more scheduled serum creatinine measurements to calculate the eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI). The exclusion criteria included patients on chronic dialysis, eGFR < 15 mL/min/1.73 m^2 or with prior kidney transplantation. Those with incomplete follow-up data or insufficient serum creatinine measurements were excluded. Measurements during acute decompensated HF, dialysis initiation, or postrenal transplant were disregarded. Follow-up visits were performed after 1 month and then every 3 months thereafter, as previously described in detail [12–14]. During the first visit, patients provided written informed consent for the use of their clinical data for research purposes. The study was performed in compliance with the law protecting personal data in accordance with the international guidelines on the clinical investigation of the World Medical Association's Declaration of Helsinki. Fatal events were identified from electronic health records or by contacting patients' relatives. Data were verified by accessing data from the Catalan and Spanish Health Systems and the Spanish Death Registry (INDEF) databases. Events were adjudicated by staff of the HF clinic, and an ad hoc committee of 3–4 members chaired by J.L., who resolved all discrepancies.

Type 2 diabetes diagnosis

A diagnosis of T2D was made when at least one of the following criteria was met: (1) a diagnosis of T2D was previously established and recorded in the patient's electronic history; (2) fasting plasma glucose level ≥ 126 mg/dL or haemoglobin A1C level ≥ 6.5% identified by laboratory testing; or (3) had a current prescription for oral hypoglycaemic medication or insulin. Optimal glycaemic control was considered when more than 70% of each patient's HbA1c measurements were ≤ 7.5%.

Estimated glomerular filtration rate

Analytical blood tests with creatinine measurements were scheduled at baseline, at 1 month and every 3–6 months thereafter during routine scheduled visits. Only scheduled creatinine measurements were included in the study. Urgent renal function assessments and very outlier values (creatinine > 10 mg/dL and < 0.1 mg/dL) as well as measurements taken after initiating dialysis treatment or receiving a renal transplant were discarded [11]. Serum creatinine levels were analysed using the Siemens CREA method (ref FD33A) on a Dimension® RxL Clinical Chemistry System (Siemens, Newark, USA) and since 2016 by enzymatic reaction on an AU5800 analyser (Bekman Coulter, Ireland). The creatinine values obtained before 2011 were standardized according to the IDMS reference method recommended by the manufacturer (Technical Bulletin: Correlation factors for correlating Jaffe creatinine methods to the IDMS creatinine reference procedure, D-01674 Siemens Healthcare Diagnostics, Inc., March 2011, rev1.0). To obtain standardized creatinine values, the following equation was applied: standardized creatinine values (mg/dL) = 1.00 × Dimension® RxL creatinine values (mg/dL)—[0.168]. The estimated GFR was calculated using CKD-EPI [15].

Statistical analysis

Categorical variables are expressed as absolute numbers and percentages. Continuous variables are expressed as the mean (standard deviation [SD]) or median (interquartile range) according to normal or nonnormal distributions. Normal distribution was assessed with normal Q-to-Q plots. Because the data followed a normal distribution, we used the t test to compare baseline eGFRs between two groups and ANOVA for comparisons across more than two groups. Loess (locally weighted error sum of squares) curves adjusted by follow-up time were plotted for the whole cohort and prespecified subgroups (sex, ischaemic aetiology, diabetes, HF classification on the basis of left ventricular ejection fraction (LVEF), age quartiles, HF hospitalizations, and vital status at the end of follow-up). Missing values due to loss to follow-up were assumed to be randomly distributed. Linear mixed effects (LME) models were used to evaluate and

compare the effect of time over the eGFR change for the total cohort and the prespecified subgroups. Random intercepts LME models were fitted on the basis of the assumption that there are important individual-level effects and that patients have similar rates of change over time. Multivariate longitudinal Cox regression analyses adjusted for baseline eGFR were performed to assess the prognostic role of eGFR trajectories on all-cause death and cardiovascular death. The Cox regression model was adjusted for the following baseline variables: baseline eGFR, age, sex, ischaemic aetiology, hypertension, LVEF, and treatments including angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), ARNI, mineralocorticoid receptor antagonist (MRA), and beta blockers. Statistical analyses were performed using SPSS 24 (SPSS Inc., Chicago, Illinois) and R (A Language and Environment for Statistical Computing) by the R Core Team (R Foundation for Statistical Computing, Vienna, Austria 2017). For the GLME models, we used the nlme R package, version 3.1–131, by Pinheiro, Bates, DebRoy, Sarkar and R Core Team (2017). A two-sided p value < 0.05 was considered significant.

Results

A total of 3,117 consecutive patients visited for the first time from August 2001 to December 2021. Among them, 2,672 patients (86%) met the criteria of not having undergone a renal transplant, not being on dialysis, eGFR ≥ 15 mL/min/1.73 m^2, and having multiple (at least two) scheduled creatinine measurements. Fifty-five patients were adequately censored when they initiated dialysis (n = 40) or were lost for blood analysis data when they moved to live outside Catalonia (n = 15).Within this cohort, there were 1,114 patients with HF who had T2D at baseline. Table 1 shows the baseline characteristics of the studied cohort. The mean age of the entire cohort was 69.3 ± 10.3 years, and 68.2% were men. The main aetiology of HF was ischaemic heart disease (57.8%), with a greater percentage of subjects presenting with depressed systolic function (74%) (LVEF ≤ 40%). With respect to metabolic comorbidities, a high proportion of the patients were overweight/obese (74%) or had hypertension (74.3%).

Out of 17,084 valid creatinine values from T2D patients, 10,830 obtained at scheduled visits were included in the analysis, with a mean of 15.8 ± 9.4 values per patient [median 4, IQR 8–22] and a range between 2 and 40 (Supplementary Fig. 1). At baseline, the mean eGFR was 61 ± 26.1 ml/min/1.73 m^2, and 52% of patients had an eGFR < 60 ml/min/1.73 m^2. The dynamic trajectory of the eGFR in patients with T2D and HF is illustrated in Fig. 1. During the 15-year follow-up period, the eGFR progressively decreased, with a slope of – 2.03 (95%

Table 1 Demographic, clinical, and therapeutic characteristics of heart failure patients with type 2 diabetes

	Total Cohort	N
Age, years	69.3 ± 10.3	1114
Male	760 (68.2)	1114
Caucasian	1091 (97.9)	1114
BMI (kg/m^2)	28.5 ± 5.2	1102
BMI category		1102
Underweight (BMI < 18.5)	6 (0.5)	
Normal (BMI 18.5–24.9)	273 (24.5)	
Overweight (BMI 25–29.9)	458 (41.1)	
Obese (BMI ≥ 30)	365 (32.8)	
HbA1c, %*	6.9 [6.1–7.9]	
Heart rate, bpm	70 [62–80]	
Systolic BP, mmHg	128.8 ± 22.4	
Hypertension	695 (74.3)	
Haemoglobin, g/dL	12.6 ± 1.8	1110
Atrial fibrillation/flutter	204 (21.8)	1114
Ischaemic aetiology	540 (57.8)	1114
HF duration, months	8 [2–48]	1114
NYHA class		1112
I	40 (3.6)	
II	756 (67.9)	
III	308 (27.6)	
IV	8 (0.7)	
LVEF, %	35.5 ± 13.7	1114
HF Classification		1114
LVEF ≤ 40%	824 (74.0)	
LVEF 41–49%	117 (10.5)	
LVEF ≥ 50%	173 (15.5)	
NTproBNP, ng/L	1789 [821–3849]	865
Creatinine (mg/dL)	1.18 [0.90–1.53]	1114
Baseline eGFR (ml/min/1.73 m^2)	61 ± 26.1	1114
CKD stages at baseline		1114
≥ 90 ml/min/1.73 m^2	179 (16.1)	
60–89 ml/min/1.73 m^2	349 (31.3)	
45–59 ml/min/1.73 m^2	237 (21.3)	
30–44 ml/min/1.73 m^2	226 (20.3)	
15–29 ml/min/1.73 m^2	123 (11.0)	
HF Treatments (Follow-up)		1114
ACEI or ARB	914 (82.0)	
Beta-blocker	1022 (91.7)	
MRA	758 (68.0)	
Loop diuretic	1065 (95.6)	
Digoxin	494 (44.3)	
Ivabradine	284 (25.5)	
ARNI	258 (23.2)	
SGLT2i	267 (24.0)	
CRT	135 (12.1)	
ICD	159 (14.3)	
Antidiabetic treatments (Follow-up)		1114

Table 1 (continued)

	Total Cohort	N
Oral drugs	917 (82.3)	
Insulin	675 (60.6)	

Values are mean ± standard deviation, *n* (%), or median [interquartile range]. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BP, blood pressure; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association. *Median of 9,223 values obtained at baseline and during follow-up

CI − 2.11 to − 1.95) ml/min/1.73 m^2 per year, p < 0.001 for trajectory changes).

Factors influencing the decline in estimated glomerular filtration rate during follow-up

The decline in the estimated glomerular filtration rate (eGFR) is influenced by several factors, including the following:

Sex and age

The baseline characteristics of patients with HF and T2D categorized by sex are shown in Supplementary Table 1. Compared with men, women tended to be older and had a higher incidence of hypertension and obesity. Notably, women demonstrated significantly elevated HbA1c levels compared with men. Moreover, a greater percentage of women than men are diagnosed with heart failure with preserved ejection fraction (HFpEF). With respect to pharmacological treatment, men were more likely to receive ARNI therapy than women were. With respect to glucose-lowering treatment, women were treated more frequently with insulin than men were at the follow-up period.

Regarding kidney function, women presented a lower baseline eGFR than men did (56.6 ± 25.5 ml/min/1.73 m^2 vs. 63.1 ± 24.6 ml/min/1.73 m^2, p < 0.001), with a greater prevalence of advanced stages of renal failure (eGFR < 30 ml/min). During follow-up, women exhibited a significantly greater decline in the eGFR than men did (slope − 2.26 [95% CI − 2.43 to − 2.10] vs. − 1.95 [95% CI − 2.05 to − 1.85], p = 0.001) (Fig. 2).

Next, we investigated the relationships among age, sex and the trajectory of the eGFR. Among patients ≥ 50 years old, women had a significantly greater decrease in the eGFR during the follow-up period than men did (slope − 2.26 [95% CI − 2.43 to − 2.09] vs. slope − 1.92 [95% CI − 2.03 to − 1.82], p = 0.003). However, the trajectory of eGFR decline was comparable between young women and men (< 50 years old) (slope − 1.21 [95% CI − 2.61 to 0.18] vs. slope − 0.77 [95% CI − 1.45 to − 0.098], p = 0.94).

HF aetiology and duration

The baseline characteristics of the study population stratified by HF aetiology (ischaemic vs. nonischaemic) are presented in Supplementary Table 2. Compared to nonischaemic aetiology, patients with an ischaemic aetiology of HF were older, with a greater proportion of male individuals. Comorbidities such as obesity or atrial fibrillation were more common in nonischaemic aetiologies, and a greater percentage had HFpEF. With respect to pharmacological treatment, ischaemic aetiologies are treated more frequently with loop diuretics and beta blockers.

No differences were detected in the eGFR at baseline when the ischaemic aetiology of HF was compared with the nonischaemic aetiology of HF (60.6 ± 24.6 ml/min/1.73 m^2 vs. 61.5 ± 25.6 ml/min/1.73 m^2, p = 0.16). However, during the follow-up period, a significantly greater decrease in the eGFR was observed in patients with nonischaemic aetiology (slope − 2.16 [95% CI − 2.29 to − 2.04] vs. − 1.92 [95% CI − 2.04 to − 1.81], p = 0.006). The dynamic trajectories of the eGFR based on HF aetiology are illustrated in Supplementary Fig. 2.

On the other hand, patients with a longer duration of HF (> 12 months) at the baseline visit experienced a more pronounced decline in eGFR than did those with newly diagnosed HF (≤ 12 months) did (slope − 2.17 [95% CI − 2.30 to − 2.05] vs. − 1.92 [95% CI − 2.03 to − 1.81], p = 0.003). Importantly, the former group also had a worse baseline eGFR of 57.9 ± 23.6 ml/min/1.73 m^2 compared to 63.3 ± 26 ml/min/1.73 m^2 in the newly diagnosed group (p < 0.001).

LVEF classification

The baseline characteristics of the study population, categorized by LEVF, are illustrated in Supplementary Table 3. The baseline eGFR was notably worse in patients with HFpEF and a mildly reduced ejection fraction (HFmrEF) than in those with HF with a reduced ejection fraction (HFrEF), with higher proportions of patients exhibiting advanced renal disease. Figure 3 shows the trajectory of eGFR according to LEVF phenotypes. Although patients with HFpEF showed a slightly greater decline in the eGFR during the follow-up period than did those with HFrEF did, the difference did not reach statistical significance (slope − 2.13 [95% CI − 2.43 to − 1.83] vs. − 1.96 [95% CI − 2.05 to − 1.86], p = 0.51). However, during follow-up, a more pronounced decrease in the trajectory of the eGFR was noted among patients with HFmrEF than among those with HFrEF or HFpEF (slope: − 2.66 [95% CI − 2.94 to − 2.38], p < 0.001 and p = 0.03, respectively).

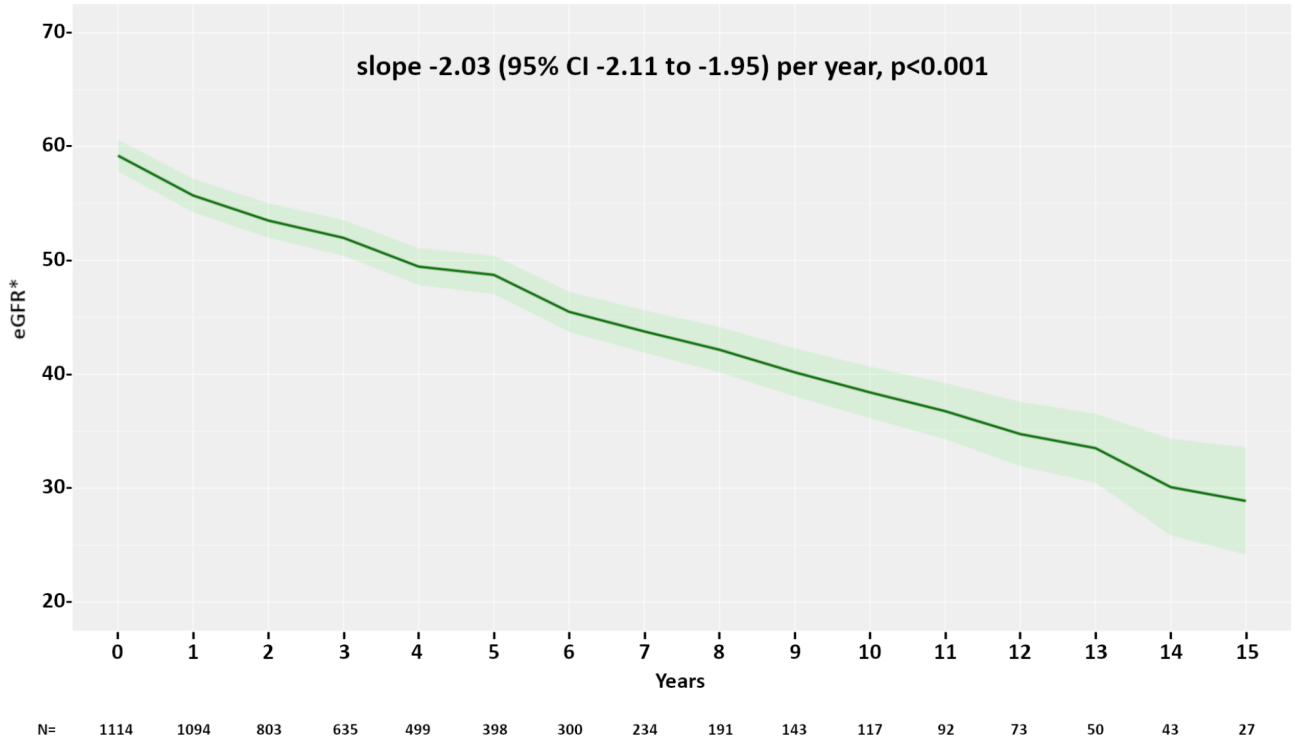


Fig. 1 Loess spline curves of long-term eGFR trajectories in patients with heart failure and type 2 diabetes. The overall decline in eGFR is evident, with a mean slope of -2.03 ml/min/1.73 m^2 per year. Shaded regions displayed around curves represent the confidence interval at a level of 0.95. *ml/min/1.73 m^2. N = number of patients at baseline and during the follow-up period

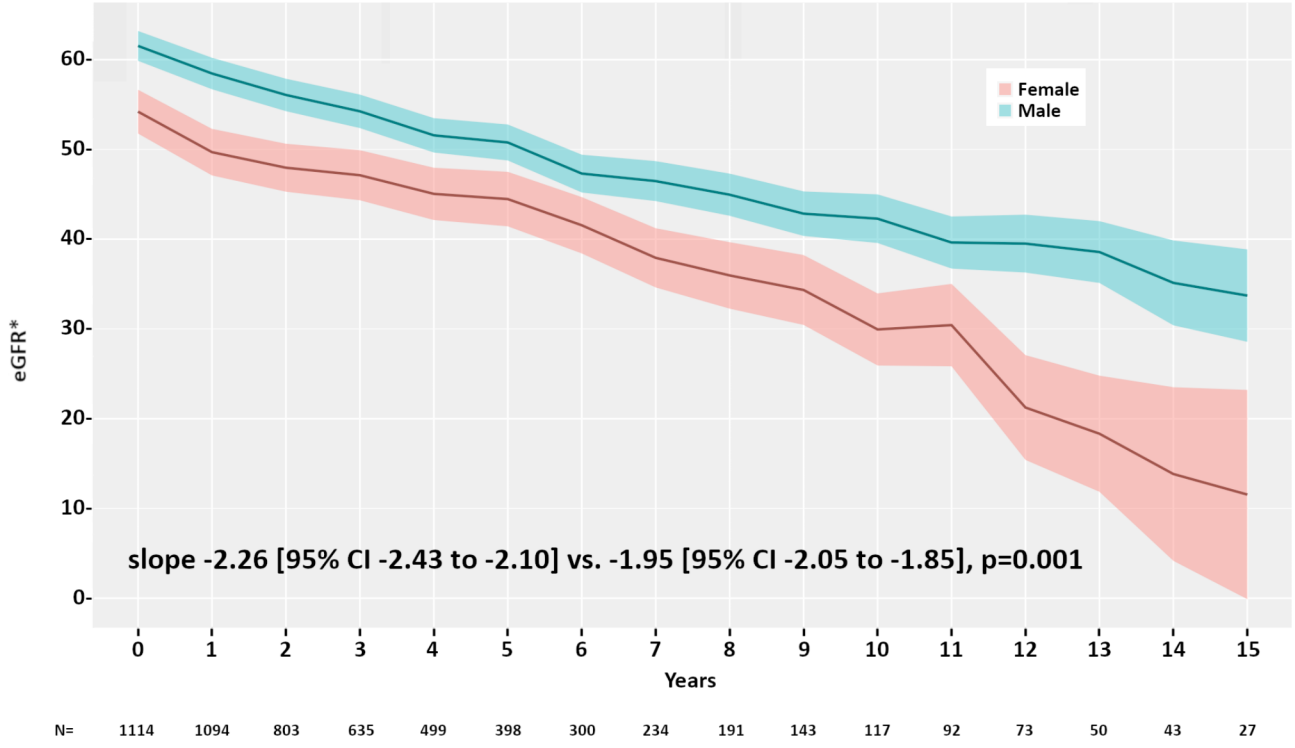


Fig. 2 Loess spline curves of long-term eGFR trajectories by sex in patients with heart failure and type 2 diabetes. Women (red) had a steeper decline in eGFR compared to men (blue). P = 0.001 for differences in trajectory changes between groups. The shaded regions around the curves represent the confidence interval at a level of 0.95. *ml/min/1.73 m^2. N = number of patients at baseline and during the follow-up period

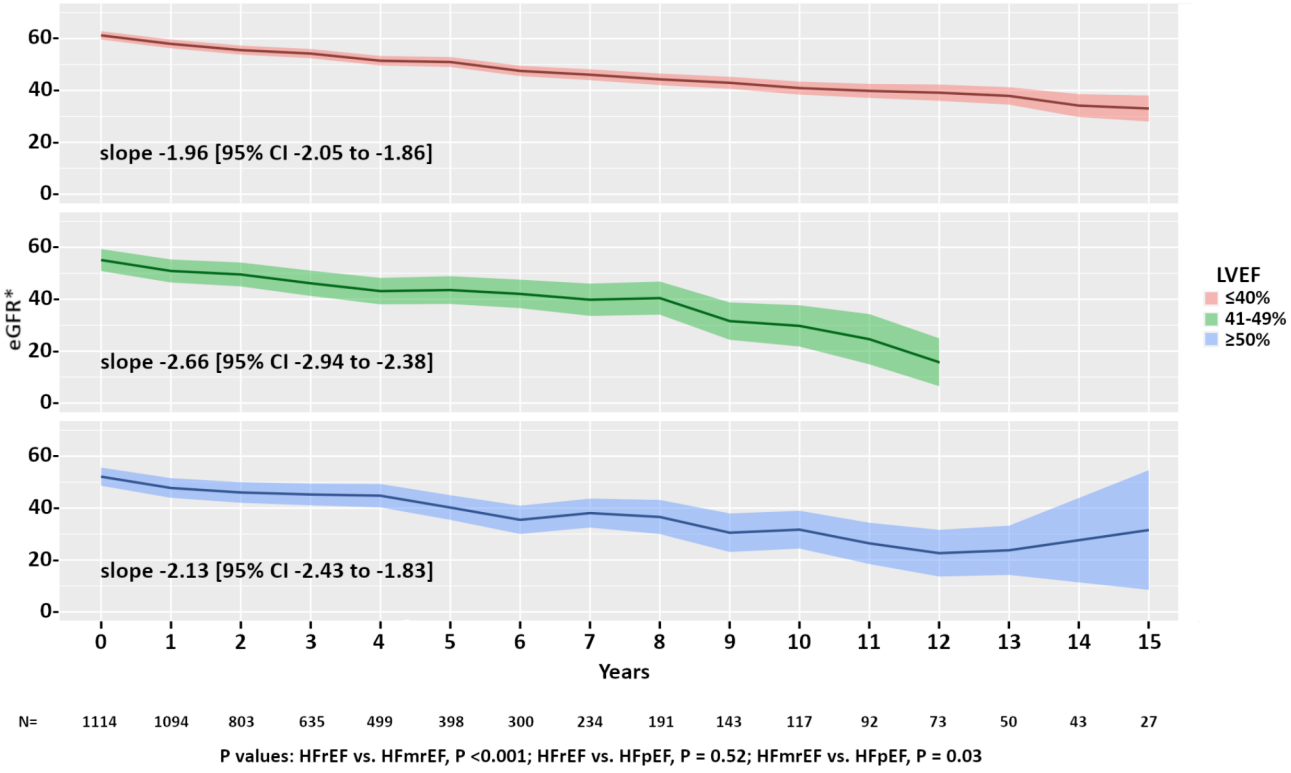


Fig. 3 Loess spline curves of long-term eGFR trajectories based on left ventricular ejection fraction (LVEF) classification. Patients with HFrEF (red) had a slower decline in eGFR than did those with HFmrEF (green) and HFpEF (blue). P values for differences in trajectory changes between groups: HFrEF vs. HFmrEF, P < 0.001; HFrEF vs. HFpEF, P = 0.52; HFmrEF vs. HFpEF, P = 0.03. Shaded regions displayed around curves represent the confidence interval at a level of 0.95. *ml/min/1.73 m^2. N = number of patients at baseline and during the follow-up period

Metabolic factors

Body mass index At baseline, obese patients had a significantly greater eGFR than did both normal weight patients (63.3 ± 25.4 ml/min/1.73 m^2 vs. 59.2 ± 23.7 ml/min/1.73 m^2, p = 0.02) and overweight patients (60.1 ± 25.3 ml/min/1.73 m^2, p = 0.04). Figure 4A illustrates the relationship between the eGFR trajectory and the baseline BMI. During the follow-up period, patients classified as obese (BMI ≥ 30 kg/m^2) presented a significantly greater decline in the eGFR (slope − 2.28 [95% CI − 2.43 to − 2.13]) than those categorized as overweight (slope − 1.85 [95% CI − 1.98 to − 1.72], p < 0.001). Although obese patients showed a slightly more pronounced decline in eGFR during the follow-up period compared to those with normal weight (slope − 2.05 [95% CI − 2.22 to − 1.87], p = 0.11), this difference was not statistically significant.

Arterial hypertension At baseline, patients with arterial hypertension presented a worse eGFR than did those without hypertension (58.7 ± 24.7 ml/min/1.73 m^2 vs. 68.3 ± 25 ml/min/1.73 m^2, respectively, p < 0.001), with a notably more substantial decline in the trajectory of eGFR (slope − 2.22, [95% CI − 2.32 to − 2.11] vs. − 1.72 [95% CI − 1.86 to − 1.58]), p < 0.001) (Fig. 4B).

Glycaemic control In terms of the degree of glycaemic control, patients with nonoptimal diabetes control had a significantly greater decline in the eGFR than did those with optimal glycaemic control during follow-up (slope − 2.23, [95% CI − 2.36 to − 2.10] vs. − 1.89, [95% CI − 2.00 to − 1.77]), p < 0.001) (Fig. 4C), although there were no differences between the two groups at baseline (62.2 ± 25.9 ml/min/1.73 m^2 vs. 60.7 ± 25 ml/min/1.73 m^2, respectively, p = 0.19).

Baseline eGFR categories

Supplementary Fig. 3 depicts the correlation between eGFR trajectories and baseline eGFR categories. The results suggest that as the baseline eGFR increases, the decline in the eGFR becomes more prominent. Specifically, for different baseline eGFRs, the following slopes were observed: 15–29 mL/min/1.73 m^2, slope − 0.57 (95% CI − 0.99 to − 0.15); 30–59 mL/min/1.73 m^2, slope − 1.43 (95% CI − 1.60 to − 1.27); 60–89 mL/min/1.73 m^2, slope − 2.23 (95% CI − 2.36 to − 2.11); and ≥ 90 mL/min/1.73 m^2, slope − 2.50 (95% CI − 2.67 to − 2.33). Significant differences in the rates of decrease in the eGFRs were noted among nearly all the groups (p < 0.001).

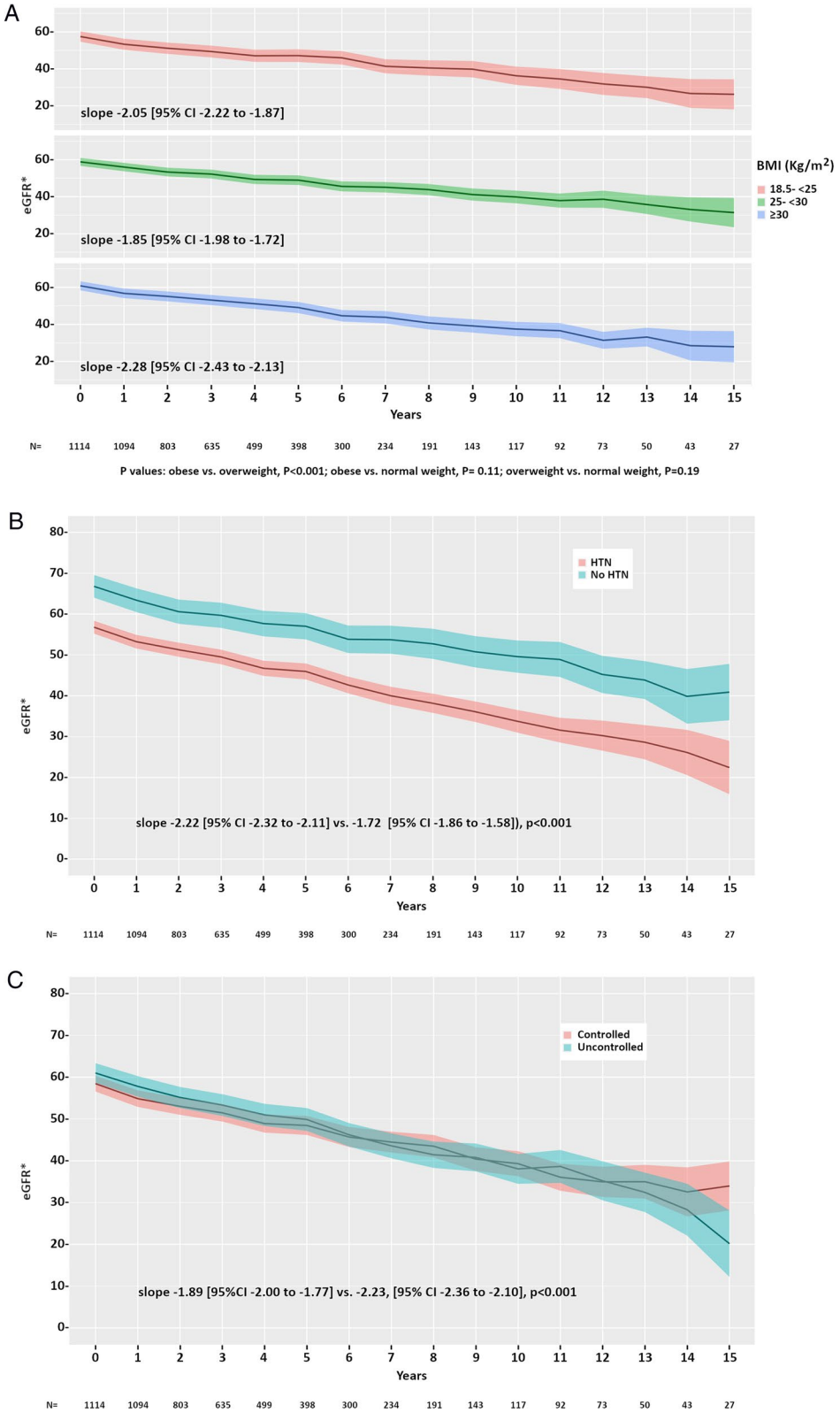


Fig. 4 (See legend on next page.)

(See figure on previous page.)

Fig. 4 Loess spline curves of long-term eGFR trajectories by baseline body mass index (BMI), hypertension status, and glycaemic control. Panel **A**: Obese patients (blue) showed a steeper decline than overweight (green) and normal-weight patients did (red). P values for differences in trajectory changes between groups: obese vs. overweight, P < 0.001; obese vs. normal weight, P = 0.11; overweight vs. normal weight, P = 0.19. Panel **B**: Patients with hypertension (red) had a more pronounced decline in the eGFR than did those without hypertension (blue). P < 0.001 for slope differences. Panel **C**: Patients with poor glycaemic control (blue) presented a greater decrease in the eGFR than did those with optimal glycaemic control (red). Optimal glycaemic control was defined as more than 70% of HbA1c values ≥ 7.5%. P < 0.001 for differences in trajectory changes between groups. The shaded regions around the curves represent the confidence interval at a level of 0.95. *ml/min/1.73 m^2. N = number of patients at baseline and during the follow-up period

HF hospitalization during follow-up

Patients were stratified according to the number of HF hospitalizations during the follow-up period into the following groups: none or more than one. Among the patients, 703 patients did not experience any HF hospitalization, and 411 required one or more HF hospitalizations. The analysis revealed that the decline in eGFR was significantly lower in patients who did not experience any HF hospitalization (slope − 1.66 [95% CI − 1.78 to − 1.55]) than in those with more HF hospitalizations (slope − 2.50, 95% CI − 2.63 to − 2.37; p < 0.001) (Fig. 5).

Pharmacological treatment

At follow-up, patients not treated with ARNIs experienced a significantly greater decline in the eGFR compared to those receiving this treatment (slope − 2.11 [− 2.21 to − 2.01] vs. − 1.83 [1.99 to − 1.67], p = 0.004) (Supplementary Fig. 4). Notably, only 6% of the patients received ARNIs at baseline, whereas 23.2% received ARNIs during follow-up. Furthermore, there were no significant differences between patients treated with a MRAs and those who did not receive this treatment (slope − 2.06 [− 2.15 to − 1.96] vs. − 1.95 [− 2.15 to − 1.75], p = 0.346).

Relationship between trajectories of kidney function and overall mortality

Over a mean follow-up period of 4.12 ± 3.7 years (median 3, IQR 1.25–6 years), with a maximum follow-up of 15 years, a total of 636 deaths were documented. Comparisons between patients who died during the follow-up period and those who survived revealed significantly lower baseline eGFR values in the deceased group (54.5 ± 24.3 mL/min/1.73 m^2) than in the surviving group (63.9 ± 25.2 mL/min/1.73 m^2, p < 0.001). Furthermore, the trajectory of eGFR decline exhibited a significantly steeper slope in patients who died (slope − 2.32, 95% CI − 2.45 to − 2.19) in contrast to those who survived (slope − 1.84, 95% CI − 1.95 to − 1.72, p < 0.001).

In the multivariable longitudinal Cox regression analyses adjusted for baseline eGFR, various factors were taken into account, including age, sex, ischaemic aetiology, hypertension, LVEF, and treatments such as angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), ARNI, mineralocorticoid receptor antagonist (MRA), and beta-blockers. The analysis revealed an independent and statistically significant association between a decrease in the eGFR during follow-up and all-cause mortality (HR 1.01, 95% CI 1.01–1.02–1; p < 0.001) (Table 2).

Discussion

This study is a post hoc analysis of previous work focused on patients with HF and T2D, providing a long-term prospective evaluation of eGFR trajectories in a real-world cohort of 1,114 patients.

Data from our study revealed that over the 15-year follow-up period, there was a consistent decline in the eGFR, with a slope of − 2.05 (95% CI − 1.66 to − 1.56) ml/min/1.73 m^2 per year. As we have previously reported this decline was notably greater compared to patients with HF who do not have T2D (− 1.56 ml/min/1.73 m^2 per year) [11]. Prior studies have shown that T2D significantly increases the risk of declining kidney function, even among patients with HF [16–18]. Compared with those without T2D, individuals with T2D experienced almost double the rate of kidney function decline. However, few studies have assessed long-term differences in kidney function decline on the basis of diabetes status [17]. Remarkably, the reported rate of eGFR decline varies across studies, depending on the baseline characteristics of the study population and baseline eGFR levels, among other factors.

In the context of HF, data from randomized control trials (RCTs), such as the EMPEROR-reduced trial, which included 3,730 patients with HFrEF (LVEF ≤ 40%; 50% had T2D), revealed that the rate of decline in the eGFR in patients with T2D was nearly twice that in patients without T2D (–2.9 versus–1.7 mL/min/1.73 m^2 per year, p = 0.02) after 16 months of follow-up [19]. Similarly, several prespecified analyses in large RCTs reported a greater rate of eGFR decline regardless of LVEF in the T2D population with HF [20–22]. In contrast, the GISSI-HF trial, which included 6.934 patients with chronic HF (41% had T2D) with a median follow-up period of 3.9 years, did not identify an interaction between time and the association of the eGFR slope in patients with T2D [23]. Compared with our T2D cohort, the GISSI-HF trial enrolled a larger proportion of male participants and had a lower prevalence of obesity and hypertension. Notably, this study excluded patients with more advanced kidney disease (baseline serum creatinine levels < 2.5 mg/dL), and

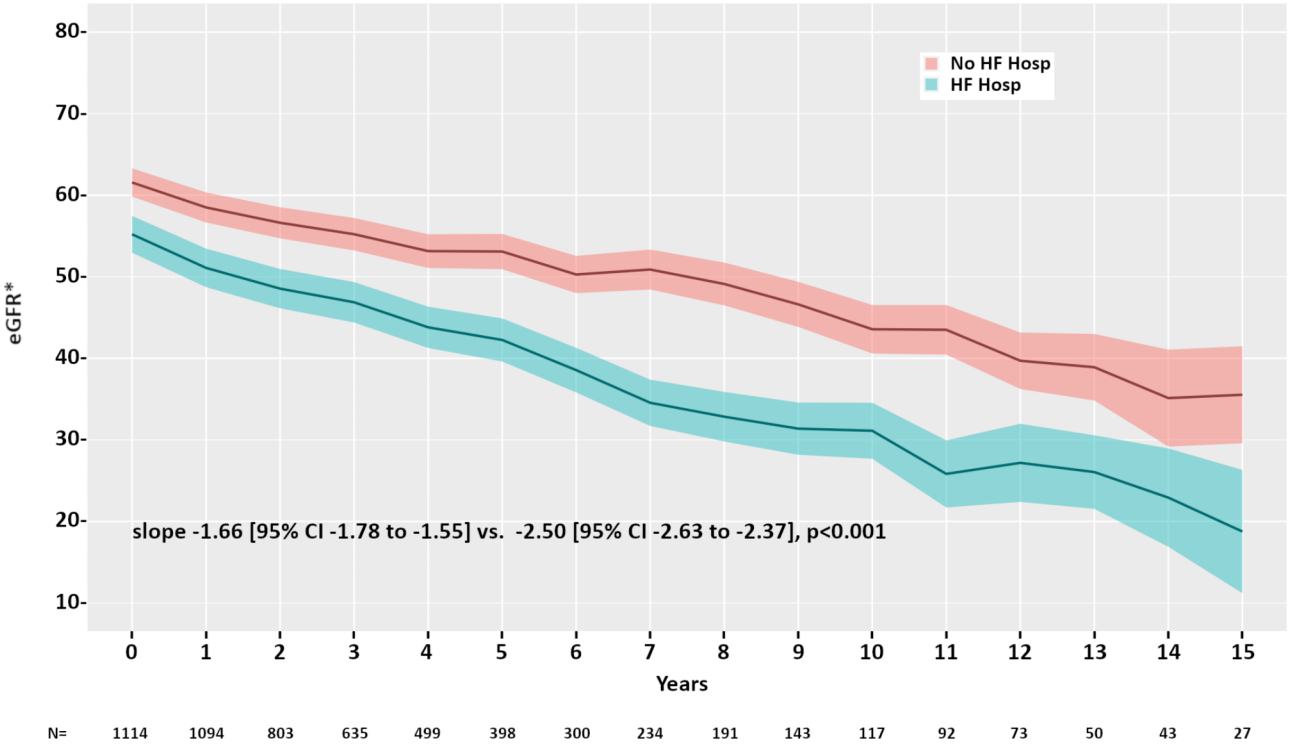


Fig. 5 Loess spline curves of long-term eGFR trajectories based on heart failure hospitalizations. Patients with one or more heart failure hospitalizations during follow-up had a steeper decline in eGFR than patients without heart failure hospitalizations did. P < 0.001 for differences in trajectory changes between groups. The shaded regions around the curves represent the confidence interval at a level of 0.95. *ml/min/1.73 m^2. N = number of patients at baseline and during the follow-up period

Table 2 Longitudinal Cox regression analysis for all-cause mortality

	HR	95%	*P*-Value
Decline in eGFR*	1.01	1.00–1.01	< 0.001
Baseline eGFR*	1.00	0.99–1.007	0.32
Age	1.03	1.02–1.04	< 0.001
Male sex	1.12	0.94–1.34	0.20
Ischaemic aetiology	1.47	1.24–1.74	< 0.001
Hypertension	1.12	0.93–1.36	0.20
LVEF‡	1.00	1.00–1.005	0.65
ACEI or ARB#	0.64	0.50–0.80	< 0.001
Beta-blockers#	0.43	0.32–0.57	< 0.001
ARNI#	0.64	0.54–0.77	< 0.001
MRA#	0.50	0.37–0.64	< 0.001

*Per 1 ml/min/1.73 m^2; ‡At baseline; #During follow-up

eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist

only 11% of the participants exhibited an LVEF > 40%, a phenotype closely related to renal failure.

Increasing evidence supports the existence of an interconnected relationship among T2D, cardiovascular dysfunction, and chronic kidney disease [4]. A comprehensive term often used to describe this interplay is cardiometabolic–renal syndrome [1]. Complex bidirectional pathophysiological interactions among these three entities have been delineated, where each independently contributes to increased incidence and exacerbates the prognosis of the others. Numerous molecular mechanisms connecting T2D to cardiorenal damage have been identified. These pathways include insulin resistance, chronic inflammation, oxidative stress, endothelial dysfunction, and dysregulation of the renin–angiotensin–aldosterone system (RAAS), among others [24–26].

Several described risk factors associated with a greater decline in eGFR in patients with T2D include age, black race, higher baseline albuminuria, high systolic blood pressure and HbA1c levels, insulin use and degrees of diabetic retinopathy, among others [4, 17]. In our study, we found that the rate of renal function decline varied among different patient subgroups and specific clinical conditions. Factors such as the interaction of sex and age, HF phenotype and aetiology, the presence of additional comorbidities such as obesity and hypertension, poor glycaemic control, higher baseline eGFR, and HF hospitalizations were associated with a more pronounced decline in renal function over time.

One of the key findings of our study was that women with HF and T2D experienced a more notable decline in the eGFR during follow-up than men did. Indeed, we observed that women had a significantly lower baseline

eGFR compared with men, which is consistent with the findings of the GISSI-HF trial [23]. In our study, women with HF and T2D were generally older and had more comorbidities, including obesity and hypertension. These patients also presented higher HbA1c levels and more frequently had preserved LVEF. These factors are also linked to a more rapid decline in the eGFR [17, 27]. Regarding sex-related differences in kidney disease, clinical studies on CKD progression in men versus women have yielded conflicting results [28]. Some studies suggest that women experience slower CKD progression than men do [29–32]. Conversely, other studies have reported no significant difference or even faster CKD progression in women [33, 34]. The cause of potential sex-related differences in CKD progression remains unclear. However, theories suggest differences in underlying risk factors, the protective effects of sex hormones, renal haemodynamics, and variances in renal mass between men and women as possible contributing factors [29].

Next, we analysed the decline in the eGFR according to both sex and age. In our cohort, older women with HF and T2D presented the greatest decline in the eGFR over time. In contrast, in the general population, Melson [35] T et al. reported that among middle-aged and elderly individuals, women experienced a slower decline in the mean eGFR than men did, regardless of health status. Conversely, it is commonly observed that premenopausal women are more protected from premature cardiovascular and other metabolic diseases than men are [36]. However, the presence of T2D seems to eliminate the survival advantage that premenopausal women without T2Dhave over men concerning CVD [37–39]. Interestingly, we found that younger hyperglycaemic women with HF had a similar trajectory of eGFR decline to that of younger men. This contrasts with several population-based studies, which generally report a more rapid decline in the eGFR in younger men than in women [16]. However, an epidemiological study by Swartling et al. revealed no significant differences in the decrease in the eGFR between men and women, both before and after the average menopausal age for women in Sweden [29]. Given the small number of premenopausal women in our cohort, these findings should be interpreted with caution. Therefore, the observed pattern may be more closely related to other clinical factors, such as comorbidities or HF characteristics, rather than the protective effect of sex hormones.

In relation to the LVEF phenotype, we found that T2D patients with HFpEF and HFmrEF had worse baseline eGFRs than those with HFrEF did, and the latter experienced a less significant decline in renal function over time. Although HFpEF patients had a slightly greater decrease in the eGFR during follow-up compared to HFrEF patients, this difference was not statistically significant. Consistent with other studies, patients with HFpEF and HFmrEF were older, had more comorbidities such as obesity and hypertension, and were in higher NYHA functional classes, contributing to a greater decline in the eGFR. Moreover, they received less treatment with ACEI, ARB, ARNI or SLGT2i, which have known nephroprotective properties. Data from previous analyses of RCTs with SGLT2i revealed that patients in the placebo group with T2D and LEVF ≥ 40% had a greater rate of eGFR decline than those with LVEF < 40%. There are few studies specifically comparing CKD across all phenotypes [18], and, in most of them, HFmrEF has either been excluded or grouped with the HFpEF or HFrEF population [18, 40–42]. Several studies have demonstrated that patients with HFpEF are more likely to have impaired renal function [18, 43]. HFpEF appears to be potentially linked to endothelial dysfunction and inflammation, which could contribute to both cardiac and renal fibrosis [44].

With respect to metabolic factors, our study revealed a significantly greater decline in renal function among patients with hypertension. This result contrasts with the findings of the GISSI-HF trial [23]. In patients with T2D, high blood pressure has previously been demonstrated to be an independent risk factor for the development and progression of diabetic nephropathy [4, 17]. Interestingly, consistent with previous research, patients with nonoptimal glycaemic control experienced a more pronounced decline in the eGFR. Data from the ARIC (Atherosclerosis Communities) study, a community-based cohort that evaluated the patterns of eGFR decline over 26 years in relation to T2D, revealed that hypertension and HbA1c levels ≥ 9% were associated with a more rapid decline in the eGFR [17].

On the other hand, we found that patients with obesity, despite a better baseline eGFR, experienced a steeper decline in the eGFR; however, this difference did not achieve statistical significance compared with those with a normal weight. Obesity is strongly related to the risk of CKD development and progression, even after adjustment for other confounding factors [45–47]. The mechanisms are complex and include haemodynamic changes, inflammation, oxidative stress, and activation of the renin–angiotensin–aldosterone system (RAAS) [48, 49]. Sufficient information on how obesity impacts the long-term progression of kidney disease in patients with HF is not available. In a prospective cohort study involving 5,887 subjects at high cardiovascular risk, those with higher BMIs experienced a greater decline in kidney function over 5 years [50]. A retrospective analysis from the ARIC study, with over 30 years of follow-up, revealed that midlife obesity was associated with a greater decline in the eGFR, particularly in women [51].

Our study revealed that ARNI treatment was linked to a slower decline in the eGFR, although only 23% of patients received this treatment during follow-up. The use of new medications for preventing and treating cardiovascular and diabetic kidney disease is an expanding research area. Large-scale clinical trials have shown that novel glucose-lowering drugs, such as SGLT2i, offer benefits beyond glycaemic control, such as reducing important renal endpoints and slowing the annual decline in eGFR in populations with and without T2D [1, 52–54]. However, the evidence for these renoprotective effects of SGLT2i in patients with HF is not as strong, possibly because of the shorter duration of the trials [55]. In our study, the recent emergence of SGLT2i therapies limited our ability to evaluate their potential long-term effects on eGFR progression.

Previous longitudinal studies, including those focusing on T2D and HF populations, have evaluated the effect of the rate of eGFR decline on the increased risk of death and cardiovascular events [23, 56–59]. In our study, the slope of the eGFR was associated with all-cause mortality during follow-up, even after adjusting for various risk factors, which is consistent with findings from other researchers [23, 58, 59]. Specifically, a 10 mL/min/1.73 m^2 decrease in the eGFR during follow-up was linked to a 10% increase in all-cause mortality. The link between increased mortality and decreased kidney function may reflect the severity of heart disease or HF progression and renal function, as kidney disease involves factors such as proinflammatory markers, arterial stiffness, dyslipidaemia, hyperhomocysteinaemia, and anaemia, which could increase mortality risk [58]. Future research should explore whether the early use of SGLT2is, which are known to reduce all-cause and cardiovascular mortality in patients with HF, might have positive effects on these outcomes.

Our findings offer valuable insights into the long-term decline in renal function. The major strengths of our study include the large cohort size, the extended follow-up period, and the repeated prospectively scheduled measurements of eGFR. We also employed linear mixed models, which offer greater robustness than standard linear regression models do, to estimate eGFR slopes and evaluate changes over time [60]. However, the generalization of these results requires caution due to several limitations. The study population mainly consisted of older patients with multiple comorbidities, limiting its applicability to younger or less comorbid HF populations. Most patients had a reduced LVEF, which may not fully represent the broader HF spectrum. Additionally, the relatively recent introduction of SGLT2is restricted our ability to evaluate their long-term renoprotective effects. Although data on urinary albumin excretion were available for some patients, it was excluded from the analysis because of its limited longitudinal availability. Moreover, clinician-driven decisions on medication adjustments, discontinuations, and reintroductions, which could have influenced renal function and outcomes, were not considered. Additionally, although we collected detailed data on medication use at baseline and during follow-up, changes in dosing or medication transitions were not specifically analysed, which may have impacted the eGFR trajectories. Despite the extended follow-up and rigorous statistical methods, the observational nature of the study means that residual confounding cannot be excluded. Furthermore, although we performed stratified analyses, no correction model for confounding variables was applied, which limits the ability to draw definitive conclusions on the independent effects of these factors. In addition, we acknowledge that patients with declining renal function may have been more likely to be lost to follow-up, introducing potential bias due to nonrandom missing data. Future research with more diverse HF populations, longer follow-up, and newer therapies is needed to confirm and extend the generalizability of our findings.

Conclusions

Our findings revealed that, within a cohort of ambulatory patients with HF and T2D, eGFRs declined progressively over the follow-up period. Several clinical factors, such as sex, age, left ventricular ejection fraction, HF aetiology, metabolic comorbidities, glycaemic control, baseline eGFR, and hospitalizations, are associated with variations in the rate of renal function decline. Further studies are needed to better understand how these factors may influence long-term renal outcomes and the role of early interventions in CKD progression.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ARNI	Angiotensin receptor/neprilysin inhibitor
BMI	Body mass index
BP	Blood pressure
CKD	Chronic kidney disease
CRT	Cardiac resynchronization therapy
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
HbA1c	Haemoglobin A1c
HF	Heart failure
HFmEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICD	Implantable cardioverter-defibrillator
iSGLT2s	Sodium glucose cotransporter 2 inhibitors
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
RCT	Randomized control trial
T2D	Type 2 diabetes

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02632-9.

Supplementary Material 1. Figure 1. Study flowchart. 10,830 scheduled creatinine measurements from 1,114 patients were availablefor the study purposes

Supplementary Material 2. Figure 2. Loess spline curves of long-term eGFR trajectories according to heart failure aetiology. Patients with nonischaemic aetiology (blue) had a steeper decline in eGFR than did those with ischaemic aetiology (red). P = 0.006 for differences in trajectory changes between groups. The shaded regions around the curves represent the confidence interval at a level of 0.95. *ml/min/1.73 m^2. N = number of patients at baseline and during the follow-up period.

Supplementary Material 3. Figure 3. Loess spline curves of long-term eGFR trajectories according to baseline eGFR categories. eGFR 15–25 ml/min/1.73 m^2 (red), eGFR 30–59 ml/min/1.73 m^2 (green), eGFR 60–89 ml/min/1.73 m^2 (blue) and eGFR≥90 (purple). The p values for the eGFR group comparisons are as follows: <30 vs. 30-59: p <0.001; <30 vs. 60-89: p<0.0001; <30 vs. ≥90: p<0.001; 30-59 vs. 60-89: p<0.001; 30-59 vs. ≥90: p <0.001; and 60-89 vs. ≥90: p=0.06. N= number of patients at baseline and during the follow-up period.

Supplementary Material 4. Figure 4. Loess spline curves of long-term eGFR trajectories according to ARNI treatment. Patients who did not receive ARNI treatment (blue) had a more pronounced decrease in the eGFR than did those who received ARNI (red). The difference in trajectory changes between groups was statistically significant (p = 0.005). The shaded regions around the curves represent the confidence interval at a level of 0.95. *ml/min/1.73 m^2. N = number of patients at baseline and during the follow-up period

Supplementary Material 5

Acknowledgements
We sincerely thank the nurses of HF unit for data collection and for their invaluable work in the unit.

Author contributions
All authors contributed significantly to the work. M.T.J, P.C, J.L, N.A and A.B.G conceived the study and design the manuscript. M.T.J and P.C wrote the manuscript. J.L, E.Z, M.D, E.S.V, A.B, M.R, C.C.G, J.S contributed to data collection. Statistical analysis was carried out by J.L. The manuscript was critically revised by M.T.J, P.C, J.L, E.Z, A.P.M.O, M.D, E.S.V, A.B, M.R, C.G.G, M.T, G.R.G, N.A and A.B.G.

Funding
Not applicable.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
During the first visit to the HF unit, patients provided written informed consent for the use of their clinical data for research purposes. The study was performed in compliance with the law protecting personal data in accordance with the international guidelines on the clinical investigation of the World Medical Association's Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Endocrinology and Nutrition and Heart Failure Clinic, Hospital Germans Trias i Pujol, Badalona, Spain
[2]Heart Failure Clinic and Cardiology Department, Hospital Germans Trias i Pujol, Badalona, Spain
[3]Department of Medicine, Universitat Autònoma de Barcelona (UAB), Carretera del Canyet s/n, 08916 Barcelona, Spain
[4]CIBERCV, Instituto de Salud Carlos III, Madrid, Spain
[5]Heart Failure Clinic and Nephrology Department, Hospital Germans Trias i Pujol, Badalona, Spain
[6]Center for Biomedical Research on Diabetes and Associated Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III, Madrid, Spain

Received: 10 November 2024 / Accepted: 5 February 2025
Published online: 05 March 2025

References

1. Marassi M, Fadini GP. The cardio-renal-metabolic connection: a review of the evidence. Cardiovasc Diabetol. 2023;22(1):195.
2. Marx N, Federici M, Schutt K, Muller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J. 2023;44(39):4043–140.
3. Maack C, Lehrke M, Backs J, Heinzel FR, Hulot JS, Marx N, et al. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. Eur Heart J. 2018;39(48):4243–54.
4. Rossing P, Persson F, Frimodt-Moller M, Hansen TW. Linking kidney and cardiovascular complications in diabetes-impact on prognostication and treatment: The 2019 Edwin Bierman Award Lecture. Diabetes. 2021;70(1):39–50.
5. Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The global epidemiology of diabetes and kidney disease. Adv Chronic Kidney Dis. 2018;25(2):121–32.
6. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35(7):455–69.
7. Turin TC, Coresh J, Tonelli M, Stevens PE, de Jong PE, Farmer CK, et al. Change in the estimated glomerular filtration rate over time and risk of all-cause mortality. Kidney Int. 2013;83(4):684–91.
8. Sohel BM, Rumana N, Ohsawa M, Turin TC, Kelly MA, Al MM. Renal function trajectory over time and adverse clinical outcomes. Clin Exp Nephrol. 2016;20(3):379–93.
9. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726.
10. Mullens W, Martens P, Testani JM, Tang WHW, Skouri H, Verbrugge FH, et al. Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2022;24(4):603–19.
11. Zamora E, Codina P, Aimo A, Lupon J, Domingo M, Troya M, et al. Trajectories of kidney function in heart failure over a 15-year follow-up: clinical profiling and mortality. JACC Heart Fail. 2024;12:849–59.
12. Zamora E, Lupon J, Vila J, Urrutia A, de Antonio M, Sanz H, et al. Estimated glomerular filtration rate and prognosis in heart failure: value of the Modification of Diet in Renal Disease Study-4, chronic kidney disease epidemiology collaboration, and cockroft-gault formulas. J Am Coll Cardiol. 2012;59(19):1709–15.
13. Santiago-Vacas E, Lupon J, Gavidia-Bovadilla G, Gual-Capllonch F, de Antonio M, Domingo M, et al. Pulmonary hypertension and right ventricular dysfunction in heart failure: prognosis and 15-year prospective longitudinal trajectories in survivors. Eur J Heart Fail. 2020;22(7):1214–25.
14. Julian MT, Alonso N, Lupon J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, et al. Long-term LVEF trajectories in patients with type 2 diabetes and heart failure: diabetic cardiomyopathy may underlie functional decline. Cardiovasc Diabetol. 2020;19(1):38.
15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
16. Toyama T, Kitagawa K, Oshima M, Kitajima S, Hara A, Iwata Y, et al. Age differences in the relationships between risk factors and loss of kidney function: a general population cohort study. BMC Nephrol. 2020;21(1):477.

17. Warren B, Rebholz CM, Sang Y, Lee AK, Coresh J, Selvin E, et al. Diabetes and trajectories of estimated glomerular filtration rate: a prospective cohort analysis of the atherosclerosis risk in Communities Study. Diabetes Care. 2018;41(8):1646–53.
18. Lofman I, Szummer K, Dahlstrom U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. Eur J Heart Fail. 2017;19(12):1606–14.
19. Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-reduced trial. Circulation. 2021;143(4):337–49.
20. Filippatos G, Butler J, Farmakis D, Zannad F, Ofstad AP, Ferreira JP, et al. Empagliflozin for heart failure with preserved left ventricular ejection fraction with and without diabetes. Circulation. 2022;146(9):676–86.
21. Mc Causland FR, Claggett BL, Vaduganathan M, Desai AS, Jhund P, de Boer RA, et al. Dapagliflozin and kidney outcomes in patients with heart failure with mildly reduced or preserved ejection fraction: a prespecified analysis of the DELIVER randomized clinical trial. JAMA Cardiol. 2023;8(1):56–65.
22. Inzucchi SE, Claggett BL, Vaduganathan M, Desai AS, Jhund PS, de Boer RA, et al. Efficacy and safety of dapagliflozin in patients with heart failure with mildly reduced or preserved ejection fraction by baseline glycaemic status (DELIVER): a subgroup analysis from an international, multicentre, double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2022;10(12):869–81.
23. Damman K, Masson S, Lucci D, Gorini M, Urso R, Maggioni AP, et al. Progression of renal impairment and chronic kidney disease in chronic heart failure: an analysis from GISSI-HF. J Card Fail. 2017;23(1):2–9.
24. Li Y, Liu Y, Liu S, Gao M, Wang W, Chen K, et al. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. Signal Transduct Target Ther. 2023;8(1):152.
25. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev. 2013;93(1):137–88.
26. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010;107(9):1058–70.
27. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014;311(24):2518–31.
28. Ricardo AC, Yang W, Sha D, Appel LJ, Chen J, Krousel-Wood M, et al. Sex-related disparities in CKD progression. J Am Soc Nephrol. 2019;30(1):137–46.
29. Swartling O, Rydell H, Stendahl M, Segelmark M, Trolle Lagerros Y, Evans M. CKD progression and mortality among men and women: a Nationwide Study in Sweden. Am J Kidney Dis. 2021;78(2):190-9 e1.
30. Halbesma N, Brantsma AH, Bakker SJ, Jansen DF, Stolk RP, De Zeeuw D, et al. Gender differences in predictors of the decline of renal function in the general population. Kidney Int. 2008;74(4):505–12.
31. Minutolo R, Gabbai FB, Chiodini P, Provenzano M, Borrelli S, Garofalo C, et al. Sex differences in the progression of CKD among older patients: pooled analysis of 4 cohort studies. Am J Kidney Dis. 2020;75(1):30–8.
32. van der Burgh AC, Rizopoulos D, Ikram MA, Hoorn EJ, Chaker L. Determinants of the evolution of kidney function with age. Kidney Int Rep. 2021;6(12):3054–63.
33. Jafar TH, Schmid CH, Stark PC, Toto R, Remuzzi G, Ruggenenti P, et al. The rate of progression of renal disease may not be slower in women compared with men: a patient-level meta-analysis. Nephrol Dial Transpl. 2003;18(10):2047–53.
34. Kronborg J, Solbu M, Njolstad I, Toft I, Eriksen BO, Jenssen T. Predictors of change in estimated GFR: a population-based 7-year follow-up from the Tromso study. Nephrol Dial Transplant. 2008;23(9):2818–26.
35. Melsom T, Norvik JV, Enoksen IT, Stefansson V, Mathisen UD, Fuskevag OM, et al. Sex differences in age-related loss of kidney function. J Am Soc Nephrol. 2022;33(10):1891–902.
36. El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, et al. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. Circulation. 2020;142(25):e506–32.
37. Brandenburg SL, Lindenfeld J, Reusch JE, Regensteiner JG. Cardiovascular risk in women with type 2 diabetes. Med Clin North Am. 2003;87(5):955–69.
38. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006;332(7533):73–8.
39. Norhammar A, Schenck-Gustafsson K. Type 2 diabetes and cardiovascular disease in women. Diabetologia. 2013;56(1):1–9.
40. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006;113(5):671–8.
41. Smith DH, Thorp ML, Gurwitz JH, McManus DD, Goldberg RJ, Allen LA, et al. Chronic kidney disease and outcomes in heart failure with preserved versus reduced ejection fraction: the Cardiovascular Research Network PRESERVE Study. Circ Cardiovasc Qual Outcomes. 2013;6(3):333–42.
42. Bonacchi G, Rossi VA, Garofalo M, Mollace R, Uccello G, Pieragnoli P, et al. Pathophysiological link and treatment implication of heart failure and preserved ejection fraction in patients with chronic kidney disease. Biomedicines. 2024;12(5):981.
43. Gori M, Senni M, Gupta DK, Charytan DM, Kraigher-Krainer E, Pieske B, et al. Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. Eur Heart J. 2014;35(48):3442–51.
44. Ter Maaten JM, Damman K, Verhaar MC, Paulus WJ, Duncker DJ, Cheng C, et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail. 2016;18(6):588–98.
45. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006;144(1):21–8.
46. Hojs R, Ekart R, Bevc S, Vodosek HN. Chronic kidney disease and obesity. Nephron. 2023;147(11):660–4.
47. Grubbs V, Lin F, Vittinghoff E, Shlipak MG, Peralta CA, Bansal N, et al. Body mass index and early kidney function decline in young adults: a longitudinal analysis of the CARDIA (Coronary Artery Risk Development in Young Adults) study. Am J Kidney Dis. 2014;63(4):590–7.
48. Jiang Z, Wang Y, Zhao X, Cui H, Han M, Ren X, et al. Obesity and chronic kidney disease. Am J Physiol Endocrinol Metab. 2023;324(1):E24–41.
49. Chen Y, Dabbas W, Gangemi A, Benedetti E, Lash J, Finn PW, et al. Obesity management and chronic kidney disease. Semin Nephrol. 2021;41(4):392–402.
50. Aiumtrakul N, Kittithaworn A, Supasyndh O, Krittayaphong R, Phrommintikul A, Satirapoj B. Association of body mass index with kidney function and mortality in high cardiovascular risk population: a nationwide prospective cohort study. Nephrology (Carlton). 2022;27(1):25–34.
51. Yu Z, Grams ME, Ndumele CE, Wagenknecht L, Boerwinkle E, North KE, et al. Association between midlife obesity and kidney function trajectories: The atherosclerosis risk in communities (ARIC) study. Am J Kidney Dis. 2021;77(3):376–85.
52. Toyama T, Neuen BL, Jun M, Ohkuma T, Neal B, Jardine MJ, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis. Diabetes Obes Metab. 2019;21(5):1237–50.
53. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.
54. The E-KCG, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2023;388(2):117–27.
55. Packer M, Siddiqi TJ, Butler J. Drugs that slow the progression of diabetic kidney disease: are renoprotective effects attenuated in heart failure? Eur Heart J. 2023;44(17):1522–5.
56. Oshima M, Jun M, Ohkuma T, Toyama T, Wada T, Cooper ME, et al. The relationship between eGFR slope and subsequent risk of vascular outcomes and all-cause mortality in type 2 diabetes: the ADVANCE-ON study. Diabetologia. 2019;62(11):1988–97.
57. Jin Q, Kuen Lam CL, Fai Wan EY. Association of eGFR slope with all-cause mortality, macrovascular and microvascular outcomes in people with type 2 diabetes and early-stage chronic kidney disease. Diabetes Res Clin Pract. 2023;205:110924.
58. Khan NA, Ma I, Thompson CR, Humphries K, Salem DN, Sarnak MJ, et al. Kidney function and mortality among patients with left ventricular systolic dysfunction. J Am Soc Nephrol. 2006;17(1):244–53.
59. Beles M, Masuy I, Verstreken S, Bartunek J, Dierckx R, Heggermont W, et al. Cardio-renal-metabolic syndrome: clinical features and dapagliflozin eligibility in a real-world heart failure cohort. ESC Heart Fail. 2023;10(4):2269–80.

60. Leffondre K, Boucquemont J, Tripepi G, Stel VS, Heinze G, Dunkler D. Analysis of risk factors associated with renal function trajectory over time: a comparison of different statistical approaches. Nephrol Dial Transpl. 2015;30(8):1237–43.