IJC Metabolic & Endocrine 4 (2014) 53–57

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

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

Giulia Russo [a,*], Giovanni Cioffi [b], Luigi Tarantini [c], Antonella Cherubini [a], Giorgio Faganello [a], Carmine Mazzone [a], Giulia Barbati [a], Riccardo Candido [d], Pompilio Faggiano [e], Andrea Di Lenarda [a]

[a] Centro Cardiovascolare, ASS1 Triestina, Italy
[b] Villa Bianca Hospital, Trento, Italy
[c] Ospedale Civile "S. Martino", Belluno, Italy
[d] Centro Diabetologico, ASS1 Triestina, Italy
[e] Spedali Civili, Brescia, Italy

ARTICLE INFO

Article history:
Received 15 May 2014
Accepted 5 July 2014
Available online 1 August 2014

Keyword:
Chronic heart failure
Systolic dysfunction
Type-2 diabetes
Chronic kidney disease
Prognosis

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

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Cardiovascular Center, ASS1 Triestina , Via Slataper 9, 34125 Trieste, Italy. Tel.: +39 0403992902; fax: +39 0403992935.
E-mail address: giulia.russo@ass1.sanita.fvg.it (G. Russo).

http://dx.doi.org/10.1016/j.ijcme.2014.07.001

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*

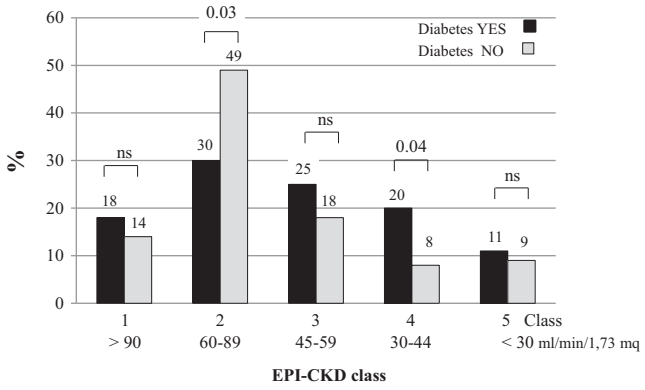

Fig. 1. Distribution of patients with type 2 diabetes mellitus according to the degree of renal dysfunction.

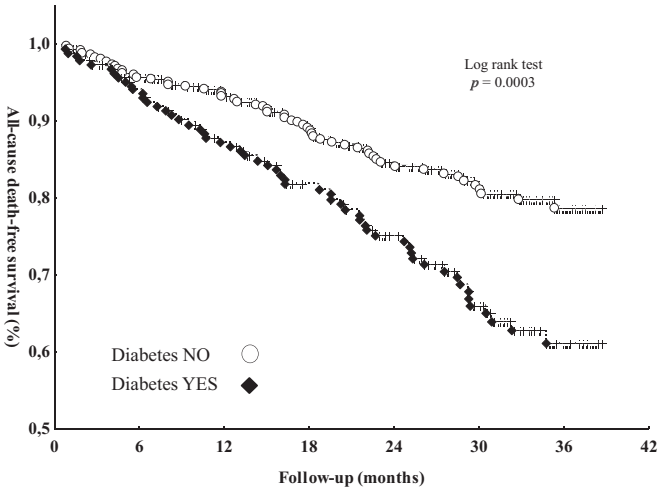

Fig. 2. All-cause death-free survival in patients with and without type 2 diabetes mellitus. Kaplan–Meier survival curves are shown and the difference between the two curves was tested for significance by the log-rank test.

3. Statistical analysis

Data are reported as mean values ± 1 standard deviation. Unpaired Student's test and χ^2 statistics were used for descriptive statistics. Between-group comparisons of continuous and normally distributed variables were performed by the analysis of variance. Kaplan–Meier survival curves were performed and the differences were tested for significance by the log-rank test. Log cumulative hazard functions were also computed by univariate and multivariate Cox proportional hazards analyses to identify the predictors of all-cause mortality (primary end-point) and probabilities of event-free survival. In the final model, along with T2DM that was included as a categorical variable, other variables included in multivariate Cox regression models were selected as possible confounding factors on the basis of their significance in univariate analyses: age, body mass index, systolic blood pressure, beta-blocker treatment, and NYHA functional class. All analyses were performed using statistical package SPSS 19.0 (SPSS Inc. Chicago, Illinois) and statistical significance was identified by two-tailed $p < 0.05$.

4. Results

The study population consisted of 554 patients whose main clinical characteristics are shown in Table 1. T2DM was diagnosed in 192 subjects (35% of total study population). Patients who had T2DM were younger, more frequently male and obese with a higher prevalence of hypertension and a worse renal function than those who had not.

As far as the echocardiographic parameters are concerned, the former presented a more severe degree of diastolic dysfunction and higher pulmonary artery systolic pressure than the latter. Moreover, patients who had T2DM were treated more aggressively with the use of anti-platelets and statins than those who had not, while the use of beta-blockers, ACEi/ARBs, diuretics, aldosterone antagonists, diuretics and digitalis was similar in the two groups both when study patients were considered all together, and when divided in various subgroups according to the degree of CKD. The distribution of patients with T2DM according to the degree of renal dysfunction is shown in Fig. 1.

During a follow-up period of 23 ± 11 months, 115 patients died (21%), 38 of them (7%) within the first year of observation. All-cause death occurred in 57 of 192 patients (30%) with T2DM and in 58 of 362 patients (16%, $p < 0.001$) without T2DM. As expected, considering the total study population, Cox regression analysis revealed that T2DM was associated with an increased risk of death (adjusted HR 2.55 [95% CI 1.02–6.36], $p = 0.04$) independently of NYHA class and the lack of beta-blocker therapy (Table 2, Fig. 2). However, when patients were grouped according to the absence or presence of renal dysfunction [defined as eGFR < 60 ml/min * 1.73 m^2] the prognostic significance of T2DM was lost (Table 3). Notably, T2DM, independently of NYHA class and beta-blocker therapy, predicted all-cause mortality in the sub-group of patients with eGFR comprised between 90 and 30 ml/min * 1.73 m^2 (adjusted HR 3.37 [95% CI 1.10–10.31], $p = 0.03$) (Table 3, Fig. 3).

5. Discussion

This study demonstrates that in out-patients with CHF the impact of T2DM of all-cause mortality is strongly influenced by the degree of CKD. We found, indeed, that whereas renal function was normal or, on the opposite side of the spectrum, renal dysfunction was severe, the presence of T2DM was non-influential on all-cause mortality. On the contrary, T2DM emerged as an independent predictor of adverse events in patients with mild–moderate CKD. These results are consistent with data recently reported by our group derived by IN-HF Outcome Registry

Table 2
Cox proportional hazard multivariate analysis for prediction of death for all cause (primary end-point).

Multivariate analysis	Dead for all cause n = 115 (21%)	Alive at follow-up n = 439 (79%)	HR	Confidence intervals	p
Diabetes mellitus	50%	31%	2.56	1.14–5.72	0.02
NYHA functional class (1–4)	2.5 ± 0.7	2.1 ± 0.6	2.55	1.33–4.96	0.005
Beta-blocker treatment	29	45	0.42	0.19–0.92	0.03
Systolic blood pressure (mm Hg)	125 ± 17	132 ± 20	0.98	0.95–1.01	0.09
Age (years)	78 ± 8	72 ± 10	1.06	0.99–1.14	0.76
Body mass index (kg/height^2)	26.6 ± 4.7	26.7 ± 4.3	1.06	0.99–1.14	0.76

Table 3
Number of events in patients with and without Diabetes and prognostic power of Diabetes on primary end-point (all-cause mortality). Analysis in the total population and in the subgroup with different degree of renal function measured as glomerular filtration rate (CPK-EPI equation).

	Number of patients	Number of deaths	Yes Diabetes	No Diabetes	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Total population	554 (100%)	115 (21%)	52/192 (30%)	58/362 (16%)	1.97 (1.36-2.84)	<0.001	2.56 (1.14-5.72)	0.02
GFR > 60 ml/min/1.73/m^2	313 (56%)	42 (13%)	16/79 (20%)	26/234 (11%)	2.06 (0.86-4.95)	0.11	0.06 (1.12-3.06)	0.54
GFR < 60 ml/min/1.73/m^2	241 (44%)	73 (30%)	46/113 (41%)	27/128 (21%)	2.34 (1.14-4.82)	0.02	2.75 (0.95-7.97)	0.60
GFR between 90 and 30 ml/min/1.73/m^2	416 (75%)	86 (21%)	55/158 (35%)	31/258 (12%)	3.20 (1.66-6.10)	<0.001	3.37 (1.10-10.31)	0.03

[9], from which patients with severe renal dysfunction hospitalized for an episode of acute heart failure were selected and analyzed. In this population, we observed that the absence, not the presence of T2DM, was a predictor of one-year mortality. Fox et al. [13] lately showed that even in less-suffering patients belonging to general population or high-risk CV cohorts, the relative risks of mortality outcomes according to lower eGFR were much the same irrespective of the presence or absence of T2DM, emphasizing the dominant role of CKD in comparison with that of T2DM as a predictor of clinical adverse events.

Three different theories might be hypothesized to explain our results: 1) the possibility that several CHF patients may develop some protective mechanisms influencing positively the outcome with a power that overcomes the negative effect of T2DM itself and/or 2) the circumstance that the negative prognostic effect of T2DM may be exhausted in patients who survived both the CHF and the severe CKD, the two major complications of T2DM and 3) the evidence that by our approach, we compared subgroups of patients with T2DM to counterparts without T2DM who belong to the same class of CKD and, consequently, who have similar contraindications to the evidence-based heart failure medications (such as ACEi/ARBs, aldosterone antagonists, diuretics, digitalis) that may influence renal function and, even more relevant, morbidity and mortality [14]. It is well-known, indeed, that the presence of CKD is associated with underuse or use at very low doses of these pharmacological therapies proportionally to the degree of CKD itself. So, these compelled behaviors might have a prognostic impact more relevant than T2DM itself.

Very few data are available on patients with severe renal dysfunction and CHF due to the exclusion of these patients from randomized studies [1,15]. Furthermore, the role of CKD on clinical outcomes of patients with T2DM who suffer from CHF has not been studied specifically. These considerations, together with the results of the present study, clearly suggest the need of analyzing patients with CHF following criteria that lead to make more homogeneous the study groups with a particular attention to the small subgroups of patients defined as "outliers", who often hold useful information for a better comprehension of the pathophysiological mechanisms which originate and sustain CHF.

6. Conclusion

Previous studies confirm that diabetes and renal dysfunction are predictor factors of increased mortality in patients with acute and chronic heart failure. Furthermore, none of them analyze whether the prognostic values of diabetes would influence the mortality inside the different classes of renal dysfunction. We analyze this aspect and we found out that diabetes is a predictor of mortality above all in the

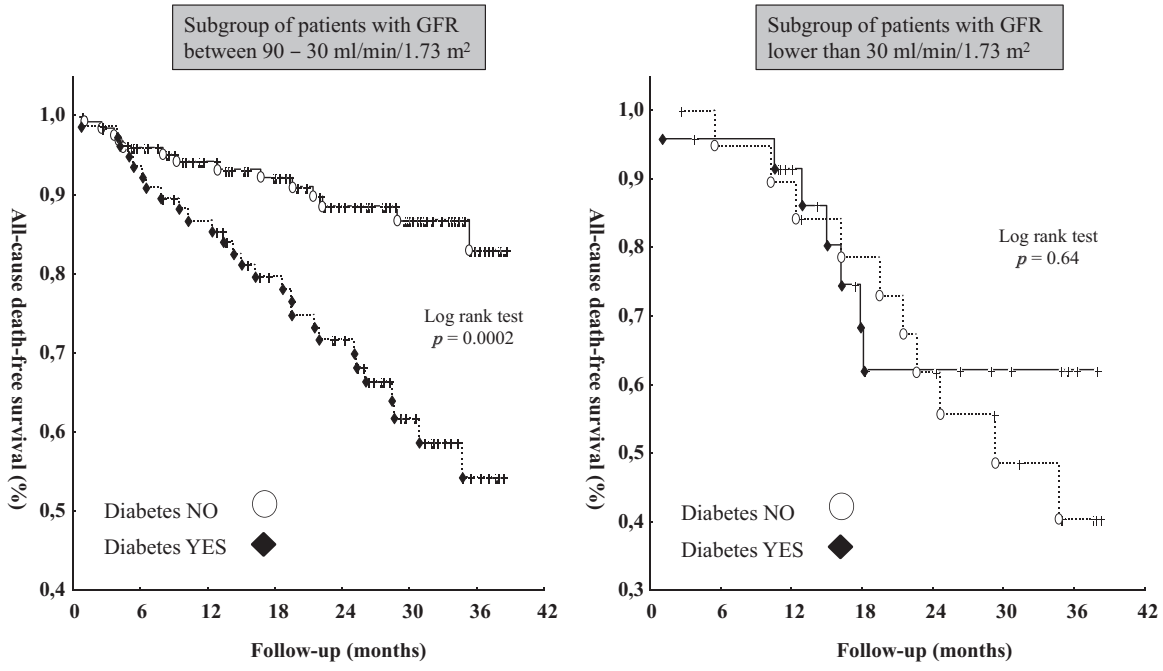

Fig. 3. All-cause death-free survival in subgroups of patients with and without type 2 diabetes mellitus with estimated glomerular filtration rate (eGFR) between 90 and 30 ml/min/1.73 m^2 (left panel) and with eGFR < 30 ml/min/1.73 m^2 (right panel). Kaplan–Meier survival curves are shown and the differences were tested for significance by the log-rank test.

mild–moderate dysfunction and its prognostic power was loss in the lowest class of renal failure.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. Eur Heart J 2012;17:2135–47.
[2] Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:681–9.
[3] Hillege HL, Nitsch D, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006;113:671–8.
[4] Van Deursen VM, Urso R, Laroche C, et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail 2014;16:103–11.
[5] From AM, Leibson CL, Bursi F, et al. Diabetes in heart failure: prevalence and impact on outcome in the population. Am J Med 2006;119:591–9.
[6] MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure. Eur Heart J 2008;29:1377–85.
[7] Cubbon RM, Adams B, Rajwani A. Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology. Diab Vasc Dis Res 2013;10:330–6.
[8] Cioffi G, Mortara A, Di Lenarda A, et al, Italian Acute Heart Failure Survey. Clinical features, and in-hospital and 1-year mortalities of patients with acute heart failure and severe renal dysfunction. Data from the Italian Registry IN-HF Outcome. Int J Cardiol 2013;168:3691–7.
[9] McMurray JJ, Adamopoulos S, Anker SD, et al, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.
[10] Levey AS, Stevens LA, Schmid CH, et al, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[11] Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al, National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–47.
[12] Ekundayo OJ, Muchimba M, Aban IB, Ritchie C, Campbell RC, Ahmed A. Multimorbidity due to diabetes mellitus and chronic kidney disease and outcomes in chronic heart failure. Am J Cardiol 2009;103:88–92.
[13] Fox CS, Matsushita K, Woodward M, et al, Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380:1662–73.
[14] Knight EL, Glynn RJ, McIntyre KM, Mogun H, Avorn J. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the studies of left ventricular dysfunction (SOLVD). Am Heart J 1999;138:849–55.
[15] Saltzman HE, Sharma K, Mather PJ, Rubin S, Adams S, Whellen DJ. Renal dysfunction in heart failure patients: what is the evidence? Heart Fail Rev 2007;12:37–47.