The prognostic value of renal dysfunction in patients with chronic heart failure: 12-month follow-up

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Abstract

Introduction: Renal function assessment is an important element of management and therapeutic decision-making in patients with chronic heart failure (CHF).

Aim: To evaluate the prognostic value of renal dysfunction in patients with CHF in 12-month follow-up.

Methods: 639 consecutive patients hospitalised in our department from 1 July 2002 to 31 December 2003 with diagnosis of CHF (NYHA II-IV), based on medical records, were initially enrolled in the study. Patients underwent one-year follow-up. Finally, 498 patients, aged 22-98 years (mean age 69 \pm 12 years) in whom creatinine concentration was measured and creatinine clearance was estimated at admission with the Cockroft-Gault quotation and with long-term follow-up results obtained, were enrolled in the study. Patients were divided into two groups according to the creatinine level: Group I without renal dysfunction (creatinine level <1.4 mg/dl), and Group II - with renal dysfunction (creatinine level >1.4 mg/dl).

Results: Patients with renal dysfunction were significantly older and more likely to be male and in NYHA class III-IV (p < 0.001). Analysis of pharmacotherapy for CHF revealed that patients with renal impairment significantly less frequently received beta-blockers (67% vs 81%, p < 0.005), angiotensin-converting enzyme inhibitors (68% vs 82%, p < 0.005) and combined treatment of β -blocker and angiotensin-converting enzyme inhibitor (56% vs 71%, p < 0.05), whereas loop diuretics were more frequently prescribed in this group (80% vs 70%, p < 0.05). In patients with renal dysfunction, there was a significantly higher mortality rate at 30 days (32% vs 14%, p < 0.001) as well as at 12 months (45% vs 20%, p < 0.001). The incidence of re-hospitalisation for cardiovascular reasons (CHF worsening, myocardial infarction, stroke) was significantly higher in patients with renal dysfunction (70% vs 55%, p < 0.005). Multivariate analysis of all factors affecting one-year mortality demonstrated that renal dysfunction is a strong and independent risk factor for death in patients with CHF (RR=2.13, 95% CI: 1.31-3.45; p < 0.05) and it increases the risk of re-hospitalisation (RR=1.53, 95% CI: 1.01-2.14; p < 0.05).

Conclusions: Renal dysfunction is an independent prognostic factor in patients with CHF, which allows identification of a high-risk group and administration of optimal therapy, which in turn can result in a reduction of mortality.

Key words: chronic heart failure, renal dysfunction, prognosis

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Introduction

Chronic heart failure (CHF) is currently one of the most frequently diagnosed cardiovascular disorders. The latest epidemiologic data show that this problem is observed in 2% of the general population, and the number of patients increases rapidly with age to reach 15% in those older than 65 years [1, 2]. Despite the introduction of mortality-reducing drugs, prognosis in

this group of patients is very unfavourable. Annual mortality depends on CHF progression and coexisting diseases and is estimated to range from 7% to 28% [1, 2].

Results of the latest large clinical trials in CHF patients revealed that impaired renal function is an independent prognostic factor. This dysfunction is observed in more than 30% of CHF patients, and mortality among them is twice as high as in those

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without renal impairment [3]. Prospective studies demonstrated that even mild or moderate renal impairment is a significant factor affecting mortality in patients with left ventricular (LV) dysfunction, acute myocardial infarction (MI) and in those who undergo cardiac surgery [4-7].

The aim of this study was to evaluate the prognostic value of renal dysfunction in patients with CHF in 12-month follow-up.

Methods

Patients

A group of 639 consecutive patients hospitalised in the First Department of Cardiology from 1 July 2002 to 31 December 2003 with diagnosis of CHF, based on medical records, were initially enrolled in the study. Inclusion criteria were: clinically evident heart failure (II-IV functional class according to the New York Heart Association), validated diagnosis by the Framingham criteria and creatinine serum level measured at admission to the hospital [8]. Patients underwent prospective one-year follow-up. Finally, 498 patients aged 22-98 years (mean age 69±12 years) who met the inclusion criteria and with long term follow-up results obtained were enrolled in the study.

All patients had echocardiographic examination performed with ejection fraction and wall motion score index (WMSI) assessment.

Renal function evaluation

In all admitted patients blood samples were taken in order to measure creatinine level. Renal dysfunction was defined as creatinine level above 1.4mg/dl. Patients were divided into two groups according to creatinine level: Group I without renal dysfunction (creatinine level <1.4mg/dl); Group II with renal dysfunction (creatinine level >1.4mg/dl). In all patients creatinine clearances was estimated with the Cockroft-Gault quotation: [(140 – age in years) x wt (kg) x 0.85 (in women)]/(72x creatinine serum level) [9].

Statistical analysis

Results are given as mean \pm standard deviation (SD) or as a percentage. Mortality and incidence of further hospitalisations for cardiovascular reasons during one-year follow-up were compared between both groups with the log-rank test and graphical curves were generated by the Kaplan-Meier method.

Cox proportional hazards analyses were done to determine factors affecting mortality and necessity of re-hospitalisation. The following factors were assessed using univariate analysis: age above 65 years, CHF aetiology (history of MI, hypertension – diagnosed when measurements above 140/90 mmHg were noted, primary valve disease, primary cardiomyopathies), coexisting diseases (diabetes mellitus - diagnosed according to the WHO criteria from 1999, anaemia - decreased haemoglobin concentration below 12 g/dl, stroke in the past, chronic obstructive pulmonary disease), CHF class according to NYHA, CHF class according to Killip-Kimball, LV systolic dysfunction defined as a reduction of LV ejection fraction below 45%, systolic blood pressure (<100 mmHg), diastolic blood pressure (<90 mmHg), heart rate (>120/min), urea level (>48 mg/dl) and potassium level (>5.5 mmol/l and <3.6 mmol/l) estimated on admission, the occurrence of arrhythmia during hospitalisation (atrial fibrillation, ventricular tachycardia, ventricular fibrillation), LBBB, treatment (B-blockers, angiotensin-converting enzyme inhibitors: ACE-I, spironolactone, digoxin, aspirin, statins and calcium channel blockers). Only factors that reached statistical significance on univariate analysis were included in multivariate analysis. Relative risk (RR) was given with 95% confidence interval (CI). A p value of <0.05 was considered significant. All analyses were performed with the SPSS statistical software package version 13.0.

Results

Basic characteristics of the study population and particular groups are presented in Table I.

Patients with renal dysfunction were significantly older and more likely to be male and in NYHA III-IV class (p < 0.001). Mean hospitalisation time was longer in Group II than in Group I, 14 versus 12 days, respectively (NS).

The incidence of CHF ischaemic aetiology was significantly higher in Group II (89% vs 81%, p <0.001). There were no differences between the two groups in the incidence of the following disorders: diabetes mellitus, hypertension, primary valvular disease, history of stroke, arteriosclerosis obliterans, chronic obstructive pulmonary disease. Past history of renal disease was more frequently noted in Group II (p <0.001). The incidence of anaemia was also significantly higher in Group II (p <0.05).

Global LV dysfunction (ejection fraction) and WMSI did not differ between the two groups (NS). Creatinine and urea concentrations, biochemical markers of renal dysfunction, were higher in Group II, which was accompanied by creatinine clearance decrease (p < 0.001). Renal impairment was associated with potassium level increase (p < 0.001), whereas sodium level was not influenced (NS).

Analysis of pharmacotherapy for CHF revealed that patients with renal impairment significantly less frequently received β -blockers (67% vs 81%, p <0.005), ACE-I (68% vs 82%, p <0.005), combined treatment with β -blocker and ACE-I (56% vs 71%, p <0.05), spironolactone

	Whole group n = 498	GROUP I n = 350	GROUP II n = 148	PP
Age [years]	69±12	67±12	73±10	<0.001
Men	63%	60%	71%	< 0.05
Body Mass Index	27±5	27±5	27±5	NS
Smoking	43%	45%	37%	NS
Duration of hospitalisation	13±10	12±10	14±11	NS
NYHA class				
П	41%	46%	28%	
	38%	36%	44%	<0.001
IV	21%	18%	28%	
CHF aetiology				
Coronary artery disease	84%	81%	89%	< 0.05
Myocardial infarction	72%	69%	80%	< 0.05
Hypertension	64%	65%	62%	NS
Primary valve disease	16%	16%	16%	NS
Primary cardiomyopathies	5%	6%	2%	NS
Coexisting diseases				
Diabetes mellitus	26%	24%	30%	NS
Renal dysfunction in anamnesis	20%	4%	57%	<0.001
Anaemia	26%	21%	39%	< 0.001
Chronic obstructive pulmonary disease	9%	9%	11%	NS
Stroke	9%	10%	7%	NS
Systolic pressure [mmHg]	130±28	130±26	129±34	< 0.05
Diastolic pressure [mmHg]	79±40	80±46	75±17	NS
Heart rate [beats/min]	86±24	85±24	88±25	NS
Ejection fraction [%]	41±12	42±11	39±12	NS
Wall Motion Score Index	1.70±0.6	1.66±0.6	1.78±0.6	NS
Creatinine serum level [mg/dl]	1.4±0.9	1.0±0.2	2.3±1.3	<0.001
Urea serum level [mg/dl]	58±35	45±16	88±25	<0.001
GFR [ml/min]	65±31	74±27	39±14	<0.001
Sodium serum level [mmol/l]	140±5	140±5	140±5	NS
Potassium serum level [mmol/l]	4.5±0.7	4.3±0.5	4.8±0.8	<0.001
Treatment				
β-blockers	77%	81%	67%	< 0.005
ACE-I	78%	82%	68%	< 0.005
β-blockers + ACE-I	66%	71%	56%	< 0.005
Digoxin	17%	18%	14%	NS
Loop diuretics	73%	70%	80%	<0.05
Thiazide diuretics	5%	6%	2%	NS
Spironolactone	38%	41%	31%	< 0.05
Aspirin	71%	72%	68%	NS
Nitrates	17%	15%	20%	NS
Statins	63%	66%	55%	< 0.05
Calcium channel blockers	12%	12%	13%	NS

Table I. Characteristics of study population and patients without (Group I) or with (Group II) renal dysfunction



Figure 1. Kaplan-Meier survival curve generated based on creatinine level in 12-month follow-up

(31% vs 41%, p <0.05), and statins (55% vs 66%, p <0.05). However, loop diuretics were more frequently prescribed in this group (80% vs 70%, p <0.05). There were no significant differences in the rate of administration of other drugs.

Thirty-day mortality was significantly higher in Group II (32% vs 14%, p <0.001). Mortality at 12 months was 45% vs 20%, respectively (p <0.001). Kaplan-Meier survival curves generated based on creatinine level and clearance are shown in Figures 1 and 2.

The incidence of re-hospitalisation for cardiovascular reasons (CHF deterioration, MI, stroke) was significantly higher in patients with renal dysfunction (70% vs 55%, p <0.005).

Multivariate analysis of all factors affecting one-year mortality demonstrated that renal dysfunction was a strong and independent risk factor for death in patients with CHF (Table II).

A similar analysis was performed in order to establish factors that increase the risk of re-hospitalisation for cardiovascular reasons during twelve months. In multivariate analysis, renal dysfunction was shown to be an independent risk factor for re-hospitalisation (Table III).

Discussion

Renal dysfunction is more and more frequently interpreted as a significant factor that worsens prognosis and accelerates CHF progression. Results of the present study in patients with symptomatic CHF indicate a high incidence of these disorders and their negative prognostic impact.

Large, randomised clinical trials revealed that renal dysfunction occurs in 30-50% of patients hospitalised



Figure 2. Kaplan-Meier survival curves generated based on creatinine clearance in 12-month follow-up

due to CHF, and the incidence increases with CHF progression [5, 10-12]. Data from observational studies indicate that the number of patients with impaired renal function may be even higher, and McAlister et al. showed in a prospective study that only 17% of CHF patients presented creatinine clearance above 90 ml/min [13].

Haemodynamic disturbances caused by cardiac dysfunction lead to significant impairment of renal blood flow and deteriorating renal function, which is in turn reflected by creatinine level increase. The PROMISE study (the Prospective Randomized Milrinone Survival Evaluation Study), which included 1088 patients, revealed that creatinine level above 1.3 mg/dl was associated with higher total mortality in patients with symptomatic CHF [14]. Results of other smaller studies also documented the prognostic value of renal dysfunction [15, 16]. The SOLVD (Studies of Left Ventricular Dysfunction) registry demonstrated the prognostic value of renal dysfunction in patients with both symptomatic and asymptomatic CHF, which also independently contributed to the progression of the disease [10]. In a large prospective observation, McAlister et al. confirmed the relationship between impaired renal function and poor prognosis in patients with systolic and diastolic CHF. A reduction of glomerular filtration rate (GFR) by 1 ml/min was associated with 1% increase in mortality [13].

In the analysed population renal dysfunction was associated with higher risk of death at 12 months, and this trend was already seen at 30 days. This confirms the assumption of this study that renal dysfunction diagnosed based on creatinine level and creatinine clearance in patients referred to the hospital due to

	Univariate analysis			Mult	Multivariate analysis		
	RR	(95% Cl)	р	RR	(95% Cl)	р	
NYHA class							
Ш	1.00			1.00			
III	2.72	(1.73-4.27)	<0.001	3.00	(1.49-6.05)	< 0.005	
IV	4.52	(2.82-7.25)	<0.001	3.25	(1.50-7.06)	<0.005	
Previous myocardial infarction	1.47	(0.98-2.20)	0.065	2.08	(1.10-3.91)	<0.05	
LVEF <45%	2.29	(1.40-3.76)	0.001	1.93	(1.05-3.56)	<0.05	
Anaemia	1.80	(1.27-2.55)	0.001	1.83	(1.09-3.09)	<0.05	
Digoxin	1.56	(1.03-2.36)	<0.05	1.87	(1.06-0.30)	<0.05	
Creatinine clearance (ml/min)							
≥60	1.00			1.00			
30-59	1.76	(1.23-2.51)	<0.005	0.81	(0.44-1.49)	NS	
<30	2.42	(1.29-4.53)	<0.01	1.63	(0.65-4.09)	NS	
Statin	0.29	(0.21-0.42)	<0.001	0.45	(0.26-0.78)	< 0.005	
ACE-I	0.26	(0.18-0.37)	<0.001	0.41	(0.23-0.72)	<0.005	
β-blockers	0.21	(0.15–0.30)	<0.001	0.36	(0.21-0.62)	<0.001	
Creatinine level (mg/dl)							
≤1.4	1.00			1.00			
>1.4	2.60	(1.86-3.64)	<0.001	2.13	(1.31-3.45)	<0.005	

Table II. Risk of death in uni- and multivariate analysis (RR value >1 indicates increased risk of death, RR value <1 indicates reduced risk of death)

CHF has great prognostic value and is a simple, cheap and widely available parameter.

Two groups can be distinguished among patients with CHF and renal dysfunction. The first group includes patients with diagnosed CHF against the background of coronary artery disease, hypertension, diabetes mellitus and atherosclerosis risk factors, in whom CHF and renal dysfunction progression influence each other and lead to disease progression. Patients from the second group before renal dysfunction did not suffer from other diseases that could lead to the development of CHF. The presence of symptomatic CHF is secondary to humoral-metabolic disturbances which occur in the course of renal dysfunction [17]. In our group no differences were found with respect to the incidence of diseases leading to renal dysfunction (with or without renal impairment). Furthermore, it is noticeable that in this study approximately 40% of patients with the most severe renal impairment had no diagnosed renal disease in the past, which provides evidence that CHF influences renal dysfunction.

A distinctive feature of patients with renal dysfunction was also the significantly higher incidence of anaemia. Levin et al. reported that haemoglobin level decrease and increase of systolic blood pressure lead to hypertrophy LV in patients with chronic renal dysfunction, which in turn accelerates CHF progression [18]. In the SOLVD study a higher mortality rate in patients with decreased haematocrit and LV dysfunction in comparison with patients with normal haematocrit was found [10]. In a group of 173 patients with symptomatic CHF, Szachniewicz et al. reported that haemoglobin level <12 g/dl in 18-month follow-up was a significant and independent prognostic factor [19]. Results of the present study confirm that patients with renal dysfunction constitute a group at particularly high risk, due to the cumulative influence of many factors that affect prognosis in patients with CHF.

It has been shown that as renal dysfunction is progressing, patients are less likely to receive drugs recommended by the European Society of Cardiology for CHF treatment, such as beta-blockers, ACE-I and combination therapy with β -blockers and ACE-I [20].

In the analysed population, administration of β -adrenergic antagonists to patients with renal dysfunction was significantly less frequent, but this percentage was significantly higher in comparison with other prospective studies. The use of β -blockers in these studies varied from 30% to 50% [21, 22]. In the CIBIS-II study (Cardiac Dysfunction Bisoprolol Study) a retrospective analysis of patients with CHF and coexisting renal dysfunction was performed.

	Univariate analysis			Mult	Multivariate analysis		
	RR	(95% Cl)	р	RR	(95% Cl)	р	
NYHA class							
II	1.00			1.00			
111	1.57	(1.18-2.07)	<0.005	1.29	(0.91-1.83)	NS	
IV	2.76	(2.00-3.82)	<0.001	2.20	(1.44-3.37)	<0.001	
Creatinine clearance [ml/min]							
≥60	1.00			1.00			
30-59	1.46	(1.13-1.87)	<0.005	1.39	(1.00-1.92)	0.051	
<30	1.76	(1.07-2.89)	<0.05	2.14	(1.12-4.13)	< 0.05	
previous myocardial infarction	1.43	(1.07-1.91)	< 0.05	1.45	(0.99-2.13)	0.056	
ACE-I	0.41	(0.32-0.54)	<0.001	0.63	(0.42-0.94)	<0.05	
β-blockers	0.39	(0.30-0.51)	<0.001	0.47	(0.31-0.70)	<0.001	
Creatinine level [mg/dl]							
≤1.4	1.00			1.00			
>1.4	1.85	(1.43-2.40)	<0.001	1.53	(1.01-2.14)	< 0.05	

Table III. Risk of re- hospitalisation in uni- and multivariate analysis (RR value >1 indicates increased risk of re-hospitalisation, RR value <1 indicates reduced risk of re-hospitalisation)

A significant mortality reduction was reported in the group treated with bisoprolol [22]. In another study, the use of carvedilol in CHF patients and renal impairment led to mortality reduction [23]. β -blockers play an important role in the treatment of patients with CHF and coexisting renal dysfunction, reducing mortality.

ACE-I are basic agents in CHF treatment. In the analysed population in the group with renal dysfunction these drugs were administrated significantly less frequently. This often results from the fact that at the beginning of ACE-I treatment a transient renal dysfunction may appear [10]. The CONSENSUS study (The Cooperative North Scandinavian Enalapril Survival Study) brought evidence for the use of ACE-I in patients with renal dysfunction. In the enalapril group significantly higher incidence of renal function deterioration defined as 30% increase of creatinine in comparison to initial measurement was observed; however, 6-month mortality rate was lower by 30% in comparison with the placebo group [11]. Results of clinical studies in the subpopulation of CHF patients with renal dysfunction indicate that this group of patients also may benefit from ACE-I use, provided careful monitoring of creatinine as well as electrolyte concentrations is ensured [11, 24]. This observation cannot be applied to patients with severe renal dysfunction, in whom creatinine clearance decreases below 30 ml/min/1.73 m².

Our results showed renal dysfunction is also an important factor affecting the necessity of further hospitalizations of CHF patients due to cardiovascular causes. In the group with renal impairment, 70% of patients needed further hospitalisations, and these were longer. In the ADHERE registry (Acute Decompensated Heart Failure National Registry) in 29% of 27,645 patients renal dysfunction was diagnosed, and more than 20% of patients had creatinine level above 2 mg/dl [25]. Patients with coexisting renal dysfunction were hospitalised more frequently, and the hospital stays were longer and generated greater costs. This could be a result of an increased tendency of fluid accumulation in extracellular space, contributing to more frequent and severe heart failure symptoms such as lower limb oedema and increasing dyspnoea. These symptoms are often the reason for admission to hospital and explain the higher frequency of use of loop diuretics in this group of patients. Careful selection of diuretics with patient self-management approach to dosing based on symptom progression would possibly improve quality of life and significantly reduce treatment costs.

Study limitations include the division of patients into groups and further analysis of the risk of death and re-hospitalisation based on a single creatinine level measurement and clearance results obtained on admission. Currently it is emphasised that in estimating prognosis dynamic changes of biochemical parameters reflecting renal function appear to be of greater importance than single measurements [26].

Despite these limitations, results of the study involving a large representative population showed that renal dysfunction represented a significant problem and how strongly it affected mortality and re-hospitalisation risk in CHF patients. The occurrence of this condition limits the administration of an optimal therapy in CHF patients, subsequently worsening prognosis in these patients. Probably more careful renal function monitoring in CHF patients would help to detect this pathology earlier and optimise therapy. Finally, it could lead to mortality reduction in the whole CHF population.

Conclusions

Renal dysfunction in patients hospitalised due to heart failure is an independent risk factor of death and necessity of further hospitalisation during 12-month follow-up.

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Znaczenie prognostyczne zaburzeń czynności nerek u pacjentów z przewlekłą niewydolnością serca – obserwacja 12-miesięczna

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Streszczenie

Wstęp: Ocena funkcji nerek jest ważnym elementem postępowania i podejmowania decyzji terapeutycznych u pacjentów z niewydolnością serca (NS).

Cel: Celem pracy była ocena wartości rokowniczej zaburzeń czynności nerek u pacjentów z NS w obserwacji 12-mies.

Metodyka: Na podstawie dokumentacji medycznej do badania wstępnie zakwalifikowano 639 kolejnych pacjentów hospitalizowanych w I Katedrze i Klinice Kardiologii w okresie od 1 lipca 2002 r. do 31 grudnia 2003 r. z rozpoznaną NS (NYHA II-IV), którzy zostali poddani obserwacji rocznej. Ostatecznie do badania włączono 498 pacjentów w wieku 22–98 lat (średnia wieku 69±12 lat), u których wykonano oznaczenie stężenia kreatyniny, w chwili przyjęcia do Kliniki wyliczono klirens kreatyniny na podstawie równania Cockrofta-Gaulta oraz uzyskano wynik obserwacji odległej. Na podstawie stężenia kreatyniny pacjentów podzielono na 2 grupy: grupa I (n=350) – bez zaburzeń czynności nerek i z stężeniem kreatyniny <1,4 mg/dl; grupa II – z zaburzeniami czynności nerek i stężeniem kreatyniny >1.4 mg/dl.

Wyniki: Pacjenci z zaburzeniami czynności nerek byli istotnie starsi, częściej płci męskiej, w klasie NYHA III–IV oraz z etiologią niedokrwienną NS (p <0,001). Analiza farmakoterapii NS u pacjentów z poszczególnych grup wykazała, że pacjenci w grupie z zaburzeniami czynności nerek istotnie rzadziej otrzymywali leki β-adrenolityczne (odpowiednio 67 vs 81%, p <0,005), inhibitory konwertazy angiotensyny (68 vs 82%, p <0,005) oraz leczenie skojarzone: β-adrenolityk oraz inhibitor konwertazy angiotensyny (56 vs 71%, p <0,05). Natomiast istotnie częściej otrzymywali diuretyki pętlowe (80 vs 70%, p <0,05). Obserwowano istotnie statystycznie wyższą śmiertelność 30-dniową (32% vs 14% vs 32%, p <0,001) oraz 12-mies. (odpowiednio 20 vs 45 %, p <0,001) w grupie pacjentów z zaburzeniami czynności nerek. Częstość ponownych hospitalizacji z powodów sercowo-naczyniowych w była wyższa w grupie pacjentów z zaburzeniami czynności nerek (50 vs 70%, p <0,005). W analizie wieloczynnikowej, uwzględniającej wszystkie parametry wpływające na śmiertelność 12-mies. wykazano, że zaburzenia czynności nerek są silnym i niezależ-nym czynnikiem ryzyka zgonu u pacjentów z NS (RR=2,13, 95% CI: 1,31–3,45; p <0,05) oraz zwiększają ryzyko ponownych hospitalizacji (RR=1,53, 95% CI: 1,01–2,14; p <0,05).

Wnioski: Zaburzenia czynności nerek są niezależnym czynnikiem prognostycznym u pacjentów z NS, pozwalają na wyodrębnienie grupy wysokiego ryzyka oraz wdrożenie optymalnej farmakoterapii co może przyczynić się do zmniejszenia śmiertelności.

Słowa kluczowe: przewlekła niewydolność serca, zaburzenia czynności nerek, rokowanie

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