			Rački
MM	AM 29.11	AI	Galley 29. 11. 2005.
SM	MG 29.11	DH	Author

Croat Med J 2005;46(6):936-941

Cardiovascular Risk Factors and Diseases Strongly Predict Hemodialysis Treatment Outcome in Maintenance Hemodialysis Patients

Sanjin Rački, Luka Zaputović[1], Božidar Vujičić[2], Žarko Mavrić[1], Mirjana Gržetić, Jagoda Ravlić-Gulan[3]

Department of Nephrology and Dialysis; [1]Department of Cardiology, Rijeka University Hospital, Rijeka; [2]General Hospital Pula, Pula; [3]Department of Physiology and Immunology, Rijeka University School of Medicine, Rijeka, Croatia

Aim To identify independent predictors of hemodialysis treatment outcome among major cardiovascular risk factors and pre-existent cardiovascular diseases in maintenance hemodialysis patients with the end-stage renal disease.

Methods A total of 144 prevalent patients on maintenance hemodialysis at Rijeka University Hospital between 1998 and 2003 were included in the prospective clinical study. Pre-existent cardiovascular risk factors and diseases were identified, as well as their relation to hemodialysis treatment outcome. Primary outcome measure was death, and secondary outcome measure was the length of time from the beginning of patient's hemodialysis treatment to the end of follow-up, ie, end of the study or patient's death. The independent variables on hemodialysis treatment outcome were identified with the multiple linear regressions.

Results Cardiovascular diseases were the major cause of death in 40 (60.6%) patients. Acute myocardial infarction in 15 (22.7%) patients was the major single cause of death. Among risk factors, hyperglycemia ($P<0.001$), low delivered dialysis dose ($P<0.001$), use of semi-synthetic dialysis membrane ($P<0.001$), and anemia ($P=0.041$) were independent predictors of hemodialysis treatment outcome. Hypertensive heart disease ($P<0.001$), ischemic heart disease ($P<0.001$), and dilated cardiomyopathy ($P=0.016$) were independent predictors of the hemodialysis treatment outcome.

Conclusions Cardiovascular diseases were the leading cause of death in hemodialysis patients. There was also high prevalence of cardiovascular risk factors and pre-existent cardiovascular diseases. Several of them were independent predictors of the hemodialysis treatment outcome.

Cardiovascular diseases are the most common cause of death among patients on the maintenance hemodialysis (1). Identification of the cardiovascular risk factors is important to devise preventive and interventional strategies. The end-stage renal disease is becoming a serious public health problem worldwide (1). In Croatia, according to the Croatian Registry for Renal Replacement Therapy, there is a substantial increase in both incident, and prevalent patients with end-stage renal disease. Most patients on the renal replacement therapy are treated with maintenance hemodialysis (76%) and have the highest mortality (15%), particularly cardiovascular (70%) (2). Cardiovascular death rates reported for patients with end-stage renal disease receiving dialysis are substantially higher than for the general population, especially for younger patients (3). Most hemo-

dialysis patients have a higher prevalence of cardiovascular risk factors compared to general population, but the relative contribution of traditional versus non-traditional risk factors for the development of pre-existent cardiovascular disease, and their influence on hemodialysis treatment outcome, remains unclear (4). We postulated that the presence of pre-existing cardiovascular risk factors and diseases at the beginning of the hemodialysis treatment predicted its outcome.

The aim of the study was to identify independent predictors of hemodialysis treatment outcome among major cardiovascular risk factors and the pre-existent cardiovascular diseases in patients with end-stage renal disease who were on maintenance hemodialysis.

Patients and Methods

This prospective study was designed to identify different variables as independent predictors of hemodialysis treatment outcome. For that purpose, we evaluated the cardiovascular morbidity and mortality and prevalence of the cardiovascular risk factors in the patients on maintenance hemodialysis. The study was conducted at the Department of Nephrology and Dialysis, Rijeka University Hospital, Rijeka, Croatia.

Patients

From January 1998 to December 2001, 194 prevalent hemodialysis patients on the maintenance hemodialysis at the Department of Nephrology and Dialysis were assessed for eligibility (Fig. 1). Only patients with end-stage renal disease who were on maintenance hemodialysis as a renal replacement therapy were included in the study. We excluded patients undergoing hemodialysis because of acute renal failure or kidney transplantation and patients undergoing peritoneal dialysis as a replacement therapy of end-stage renal disease at any time. There were 162 patients included in the study, and only 144 were analyzed at the snd pf follow-up (Fig. 1, Table 1). The patients were followed-up to December 2003.

Methods

The underlying renal disease in patients enrolled in the study was identified on the basis of the anamnestic and clinical data and previous medical records. The end-stage renal disease was defined as a permanent and irreversible loss of renal function requiring renal replacement therapy. Hemodialysis was performed three times a week for 4 hours each session. Conventional bicarbonate-buffered dialysate and either semi-synthetic (cellulose diacetate) or synthetic (polysulfone) di-

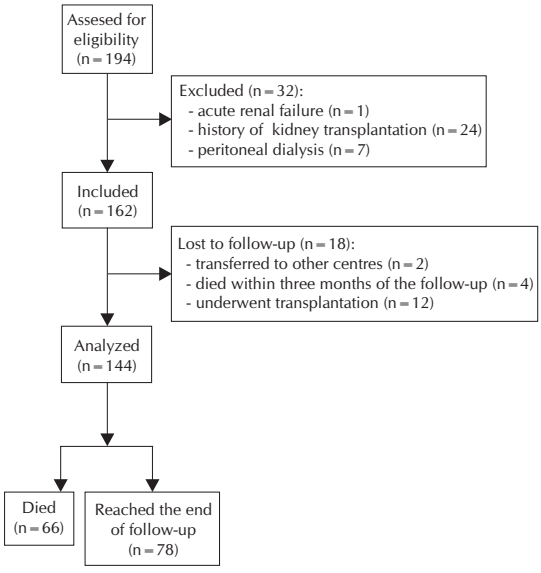

Figure 1. Flow of the patients through the study.

Table 1. Demographic characteristics, vascular access data, underlying renal diseases, and pre-existent cardiovascular diseases in patients with end-stage renal disease

Characteristic	No. (%) of patients
Sex:	
men	71 (49.3)
women	73 (50.7)
Age at the beginning of the study (years):	
≤19	1 (0.7)
20-49	16 (11.1)
50-69	61 (42.4)
≥70	66 (45.8)
Age at the beginning of hemodialysis (years):	
≤19	4 (2.8)
20-49	23 (16)
50-69	79 (54.9)
≥70	38 (26.4)
Vascular access type:	
arteriovenous fistula	114 (79.1)
arteriovenous synthetic graft	4 (2.8)
central venous catheter (permanent type)	26 (18.1)
Underlying renal disease:	
diabetic nephropathy	44 (30.6)
glomerulonephritis	30 (20.8)
vascular disease	25 (17.4)
pyelonephritis	14 (9.6)
polycystic disease	11 (7.6)
interstitial nephritis	5 (3.5)
other	15 (10.5)
Pre-existent cardiovascular diseases:	
hypertensive heart disease	90 (62.5)
ischemic heart disease	48 (33.3)
peripheral vascular disease	44 (30.6)
cerebrovascular disease	20 (13.9)
valvular disease	19 (13.2)
dilated cardiomyopathy	9 (6.3)

alysis membrane were used in all patients. The standard method of blood sampling and calculating urea reduction according to the present clinical guidelines was used to measure the delivered dialysis dose. The following procedure was used: at the end of hemodialysis session, we set ultrafiltration rate to zero, decreased the blood flow to 100 mL/min for 15 s, and than drew the blood sample from the arterial sampling port nearest to the patient. The result was calculated according to the following formula: eKt/V = spKt/V-(0.47xspKt/V/T) + 0.02. The target eKt/V value was ≥1.2. A standard procedure was used to calculate urea removal once a week (middle session), as it has been standard procedure at our Department (5,6).

The stratification of cardiovascular risk factors included identification of the traditional risk factors according to the Framingham study (7-9). High blood pressure was defined as systolic blood pressure >140 mm Hg and diastolic >90 mm Hg for three consecutive measurements starting at each hemodialysis session. Hyperglycemia was defined as fasting plasma glucose concentration >6.1 mmol/L. Hypercholesterolemia was defined as a total serum cholesterol concentration >5.0 mmol/L (10). The habit of current smoking was determined from anamnestic data. Non-traditional (uremia-related) risk factors were also determined. Anemia was defined as hemoglobin concentration <110 g/L in the presence of sufficient iron supplementation (serum ferritin concentration >100 mg/L), regardless of erythropoietin therapy. Malnutrition was defined as progressive weight loss of >5% during the three months before hemodialysis treatment, low body mass index, and serum albumin concentration <35 g/L. Hyperphosphatemia was defined as serum phosphorus concentration >1.6 mmol/L. The chronic overhydration was defined as interdialytic weight gain over three liters and inadequate "dry weight" achievement three months after beginning of hemodialysis treatment.

The pre-existent cardiovascular disease was defined according to clinical criteria and electrocardiographic (ECG), radiologic, and echocardiographic findings. The standard clinical procedure was used. Hypertensive heart disease, ischemic heart disease, dilated cardiomyopathy, valvular disease, cerebrovascular disease, and peripheral vascular disease were defined according to present clinical criteria (11).

Primary outcome measure was the patient's death as a treatment outcome and related causes of death. Secondary outcome measure was the hemodialysis treatment outcome for the patients who reached the end of the follow-up defined as a period of time from the beginning of hemodialysis treatment to the end of the study or patient's death.

A panel of three physicians reviewed and assigned an underlying cause to each patient's death. As a part of the review process, all available medical information on each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death, family members were interviewed by telephone to ascertain the circumstances of death. For the patients who reached the end of follow-up, the data of hemodialysis treatment outcome were recorded.

Statistical Analysis

All data are presented either as median and range or frequencies. Logistic regression was used to predict the hemodialysis treatment outcome based on cardiovascular risk factors and pre-existent cardiovascular diseases. Independent associations of hemodialysis treatment outcome with different variables were evaluated by stepwise multiple linear regression analysis. *P* values of <0.05 were considered significant. Statistical analysis was performed with MedCalc, release 7.5 (MedCalc, Mariakerke, Belgium).

Results

During the follow-up, 66 (45.8%) patients died, with median hemodialysis treatment duration of 25 months (range, 3-144 months). The major cause of death was cardiovascular disease in 40 (60.6%) patients. Acute myocardial infarction in 15 (22.7%) patients was the major single cause of death (Table 2). Seventy-eight (54.2%) patients reached the end of follow-up, with median duration of hemodialysis treatment of 54 months

Table 2. Major causes of death in patients with end-stage renal disese

Cause of death	No. (%) of patients
Myocardial infarction	15 (22.7)
Heart failure	13 (19.7)
Cerebrovascular disease	12 (18.2)
Sepsis	12 (18.2)
Malignant tumors	7 (10.6)
Hyperkalemia	4 (6.1)
Pneumonia	3 (4.5)

(range, 30-178 months). The overall median duration of hemodialysis treatment in this study was 41 months (range, 3-178 months). Several variables strongly influenced the hemodialysis treatment outcome.

Cardiovascular risk factors were common in patients included in the study. There was a high prevalence of both traditional and non-traditional cardiovascular risk factors. To analyze the influence of these risk factors, we performed a stepwise multiple linear regression in a model constructed with four traditional (high blood pressure, hyperglycemia, hypercholesterolemia, and current smoking), and six non-traditional (anemia, malnutrition, chronic overhydration, delivered dialysis dose, hyperphosphatemia, and use of semi-synthetic membrane) risk factors potentially related to hemodialysis treatment outcome. Four cardiovascular risk factors were independently associated with the hemodialysis treatment outcome in decreasing order of significance: hyperglycemia, semi-synthetic membrane, delivered dialysis dose, and anemia (Table 3). Other variables had no significant independent correlation with the hemodialysis treatment outcome, and were removed from the model.

Table 3. Stepwise multiple linear regression analysis of hemodialysis duration as a dependent variable on related cardiovascular risk factors*

Independent variable	β	*P*
Hyperglycemia	-2.165	<0.001
Semi-synthetic membrane	2.499	<0.001
Delivered dialysis dose	-2.912	<0.001
Anemia	-1.197	0.041

*Included variables were high blood pressure, hyperglycemia, hypercholesterolemia, current smoking, anemia, malnutrition, chronic overhydration, delivered dialysis dose, hyperphosphatemia, and use of semi-synthetic membrane. The variables were presented as categorical data, coded as 1 for present or 0 for absent. Adjusted R^2=0.309.

Cardiovascular diseases were common in the patients developing end-stage renal disease. At the beginning of hemodialysis treatment, there was a high prevalence of pre-existent cardiovascular diseases (Table 1). To analyze the influence of pre-existent cardiovascular diseases on the hemodialysis treatment outcome, we performed a stepwise multiple linear regressions, using the model constructed with six major pre-existent cardiovascular diseases observed in the hemodialysis population: hypertensive heart disease, valvular disease, ischemic heart disease, dilated cardiomyopathy, cerebrovascular disease, and peripheral vascular disease. Analysis revealed that three pre-existent cardiovascular diseases were independently associated with the hemodialysis treatment outcome in decreasing order of significance: hypertensive heart disease, ischemic heart disease, and dilated cardiomyopathy (Table 4). Other pre-existent cardiovascular diseases had no significant independent correlation with the hemodialysis treatment outcome, and were removed from the model.

Table 4. Stepwise multiple linear regression analysis of hemodialysis duration as a dependent variable on related cardiovascular diseases*

Independent variable	β	*P*
Hypertensive heart disease	-1.947	<0.001
Ischemic heart disease	-1.836	<0.001
Dilated cardiomyopathy	-2.443	0.016

*Included variables were hypertensive heart disease, ischemic heart disease, dilated cardiomyopathy, valvular disease, cerebrovascular disease, and peripheral vascular disease. The variables were presented as categorical data, coded as 1 for present or 0 for absent. Adjusted R^2=0.209.

Discussion

The main finding of our study was a significant influence of the cardiovascular risk factors and pre-existent cardiovascular diseases on the treatment outcome of the maintenance hemodialysis patients. We found that presence of hyperglycemia, anemia, low delivered dialysis dose, and use of semi-synthetic membrane strongly predict the hemodialysis treatment outcome. In addition, pre-existent cardiovascular diseases, particularly hypertensive heart disease, ischemic heart disease, and dilated cardiomyopathy, were responsible for premature patient's death.

Patients with end-stage renal disease, particularly those on hemodialysis, have a high cardiovascular mortality (12). The burden of pre-existent cardiovascular diseases and its impact on the survival of maintenance hemodialysis patients has recently received increased attention (1,13). The HEMO Study (14) also identified cardiovascular disease, particularly ischemic heart disease, to be a major cause of cardiac hospitalizations and cardiac deaths. There are many predictive factors of the hemodialysis treatment outcome. Beside the traditional cardiovascular risk factors, such as high blood pressure, hyperglycemia, and hypercholesterolemia, the progressive cardiovascular risk associated with end-stage renal disease may be explained by other factors that become increasingly important in renal decline (15-17). The most im-

portant non-traditional cardiovascular risk factors are uremia related, and include inflammation, malnutrition, progressive atherosclerosis, endothelial dysfunction, oxidative stress, anemia, hyperphosphatemia, chronic overhydration, low delivered dialysis dose, and use of semi-synthetic dialysis membranes (18-22).

An interesting finding was that low delivered dialysis dose independently predicted the hemodialysis treatment outcome. The data from large HEMO Study showed no benefits of high-targeted dialysis dose (14). As opposed to HEMO Study, Held et al (23) obtained the same results as we did.

Another interesting finding was that hypertensive heart disease, rather than high blood pressure, affected the hemodialysis treatment outcome. Obviously, hypertensive heart disease developed because of high blood pressure history and became more important than blood pressure levels in the maintenance hemodialysis patients. Also, hypercholesterolemia did not affect the hemodialysis treatment outcome. Similar findings have been recently published by Kalantar-Zadeh et al (24).

Our study had several limitations. First, we did not analyze all established cardiovascular risk factors because of missing relevant data. Second, in our nutritional evaluation, we did not use Subjective Global Assessment (SGA), as it is proposed by Dialysis Outcome Quality Initiative (DOQI) guidelines, also because of missing relevant data (25). Third, the anemia therapy with erythropoietin was not taken into account because of inconsistent drug dose. Fourth, cardiovascular diseases that developed during the follow-up were not addressed. Finally, concomitant medication was not assessed.

In conclusion, the burden of cardiovascular diseases in end-stage renal disease patients on the maintenance hemodialysis has to be prevented by early detection of cardiovascular risk factors when renal function declines. The future research has to be conducted identifying the cardiovascular risk factors, particularly uremia related, and possible treatment strategies to influence the hemodialysis treatment outcome, because the hemodialysis population carries a high risk for the cardiovascular disease, and death rates. Modern bioadequate hemodialysis could have cardioprotective effects.

References

1 National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. US Renal Data System, USRDS 2004 annual data report. Am J Kidney Dis. 2005;45(Suppl 1):8-280.

2 Croatian Society for Nephrology, Dialysis and Transplantation. Croatian registry for renal replacement therapy for the year 2003. Available from: *http://www.hdndt.org/registar_crrt03.htm*. Accessed: March 1, 2005.

3 Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32(5 Suppl 3):S112-9.

4 Culleton BF, Hemmelgarn BR. Is chronic kidney disease a cardiovascular disease risk factor? Semin Dial. 2003;16:95-100.

5 European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. Section II. Haemodialysis adequacy. Nephrol Dial Transplant. 2002;17 Suppl 7:16-31.

6 Racki S, Zaputovic L, Maleta I, Grzetic M, Mavric Z, Devcic B, et al. Assessment of hemodialysis adequacy by ionic dialysance: comparison to standard method of urea removal. Ren Fail. 2005;27:601-4.

7 Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA. 1987;257:2176-80.

8 Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation. 1979; 59:8-13.

9 Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA. 1996;275:1571-6.

10 De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003;24:1601-10.

11 McCullough PA. Interface between renal disease and cardiovascular illness. In: Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's heart disease: a textbook of cardiovascular medicine. 7th ed. St. Louis (MO): WB Saunders; 2005. p. 2161-72.

12 Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32(5 Suppl 3):S112-9.

13 Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med. 1998;339:799-805.

14 Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A, et al. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. Kidney Int. 2004;65:2380-9.

15 Anavekar NS, Pfeffer MA. Cardiovascular risk in chronic kidney disease. Kidney Int Suppl. 2004;(92): S11-5.

16 Kes P. Lipid abnormalities in chronic renal failure, nephrotic syndrome and dialysis. Acta Med Croatica. 2001;55:177-86.

17 Ravera M, Paoletti E. Hypertension, dyslipidemia and cardiovascular risk in chronic renal disease [in Italian]. Ital Heart J Suppl. 2004;5:436-44.

18 Locatelli F, Pisoni RL, Akizawa T, Cruz JM, DeOreo PB, Lameire NH, et al. Anemia management for hemodialysis patients: Kidney Disease Outcomes Qual-

ity Initiative (K/DOQI) guidelines and Dialysis Outcomes and Practice Patterns Study (DOPPS) findings. Am J Kidney Dis. 2004;44(5 Suppl 3):27-33.

19 Pecoits-Filho R, Lindholm B, Stenvinkel P. The malnutrition, inflammation, and atherosclerosis (MIA) syndrome – the heart of the matter. Nephrol Dial Transplant. 2002;17 Suppl 11:28-31.

20 Bloembergen WE, Stannard DC, Port FK, Wolfe RA, Pugh JA, Jones CA, et al. Relationship of dose of hemodialysis and cause-specific mortality. Kidney Int. 1996; 50:557-65.

21 2Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002;347:2010-9.

22 Levin NW, Gotch FA, Kuhlmann MK. Factors for increased morbidity and mortality in uremia: hyperphosphatemia. Semin Nephrol. 2004 Sep;24:396-400.

23 Held PJ, Port FK, Wolfe RA, Stannard DC, Carroll CE, Daugirdas JT, et al. The dose of hemodialysis and patient mortality. Kidney Int. 1996;50:550-6.

24 Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int. 2003;63: 793-808.

25 Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. Am J Kidney Dis. 2000 Jun;35(6 Suppl 2):S1-140.

Received: July 7, 2005
Accepted: October 7, 2005

Correspondence to:
Sanjin Rački
Department of Nephrology and Dialysis
Rijeka University Hospital Center
T. Strižića 3
51000 Rijeka, Croatia
sanjin.racki@ri.t-com.hr

Reprint Order Form

Croatian Medical Journal

To order hardcopy reprints of an article, please fill out this form and submit it to the Publisher.
Article title:_____
Issue/Year**:** _____ / _____
First (two) author(s):_____ No. of pages: ____ No. of copies: ____

	Reprint price*											
	50 copies			100 copies			200 copies			500 copies		
No. of pages of the article	HRK	EUR	USD	HRK	EUR	USD	HRK	EUR	USD	HRK	EUR	USD
1-2	324	43	39	648	85	77	688	91	82	1065	140	127
3-4	458	60	55	906	119	108	920	121	110	1397	184	166
5-8	676	89	81	1271	160	151	1330	175	158	2033	268	242
9-12	1013	133	121	1781	234	212	1958	257	233	2934	386	349
13-16	1100	145	131	2200	290	262	2344	308	279	3350	441	399
17-20	1373	181	164	2746	361	327	2816	370	335	4048	533	482
21-24	1620	213	193	3240	426	386	3379	444	402	4788	630	570

***Postage not included.**

Information on the price including postage can be obtained from the Publisher upon request. Minimum order is 50 copies.

Color illustration(s) in the reprints increase the price by 30% and are obtainable upon request submitted before the publication of the article. Reprint order received after the publication of the article is subject to a 25% surcharge.

Ship _____copies to:

_____Name _____
_____Street _____
_____City, State, Zip code_____
_____Country _____

Bill to (if different from "ship to" address):

Method of payment

1 Deposit to our bank account
Medicinska Naklada (for CMJ)
Zagrebačka banka d. d.
Paromlinska 2, 10000 Zagreb, Croatia
SWIFT: ZABA HR2X
Account No. 7001-3269167
Copy of the deposit slip should be faxed to our office.
Payment can be made in HRK or any major convertible currency.

2 Please charge my *American Express* card
Expiry date: ____ /____ /____
Card No.: _____
Signature: _____
Credit card accounts will be charged in local currency at exchange rate applicable on the date of transaction.

Medicinska naklada d.o.o. / Medical Publishing
Cankarova ulica 13, 10000 Zagreb, Croatia
Phone/fax: +385-1/ 3907 041
prodaja@medicinskanaklada.hr
www.medicinskanaklada.hr