Predictors for contrast media-induced nephropathy and long-term survival: Prospectively assessed data from the randomized controlled Dialysis-Versus-Diuresis (DVD) trial

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BACKGROUND: Among the numerous studies concerning contrast media-induced nephropathy (CIN), there was no prospective trial that provided data on the long-term outcomes.

OBJECTIVES: To prospectively assess predictors of CIN and long-term outcomes of affected patients.

METHODS: Four hundred twelve consecutive patients with serum creatinine levels of 115 µmol/L to 309 µmol/L (1.3 mg/dL to 3.5 mg/dL) undergoing elective coronary angiography were included. Patients were randomly assigned to periprocedural hydration alone, hydration plus one-time hemodialysis or hydration plus *N*-acetylcysteine.

RESULTS: Multivariate logistic regression identified the following as predictors of CIN within 72 h (equivalent to an increase in creatinine 44.2 µmol/L [0.5 mg/dL] or more): prophylactic postprocedural hemodialysis (OR 2.86, 95% CI 1.07 to 7.69), use of angiotensin-converting enzyme inhibitors (OR 6.16, 95% CI 2.01 to 18.93), baseline glomerular filtration rate (OR 0.94, 95% CI 0.90 to 0.98) and the amount of contrast media given (OR 1.01, 95% CI 1.00 to 1.01). With regard to long-term outcome (mean follow-up 649 days), multivariate Cox regression models found elevated creatinine levels at 30 days (hazard rate ratio [HRR] 5.48, 95% CI 2.85 to 10.53), but not CIN within 72 h (HRR 1.12, 95% CI 0.63 to 2.02), to be associated with increased mortality. In addition, independent predictors for death during follow-up included left ventricular ejection fraction lower than 35% (HRR 4.01, 95% CI 2.22 to 7.26), serum phosphate (HRR 1.64, 95% CI 1.10 to 2.43) and hemoglobin (HRR 0.80, 95% CI 0.67 to 0.96).

CONCLUSION: From the present prospective trial, performance of post-procedural hemodialysis, use of angiotensin-converting enzyme inhibitors, reduced baseline glomerular filtration rate and amount of contrast media were independent predictors of CIN within 72 h after catheterization. Assessing renal function after 30 days, rather than within 72 h, seemed to be more predictive for patients' long-term survival.

Key Words: ACE inhibitor; Contrast media-induced nephropathy; Hemodialysis; Mortality; Renal failure

Les prédicteurs de néphropathie induite par un agent de contraste et de survie à long terme : Des données prospectives tirées de l'essai aléatoire et contrôlé DVD sur la dialyse par rapport à la diurèse

HISTORIQUE : Parmi les nombreuses études portant sur la néphropathie induite par un agent de contraste (NIC), il n'existait pas d'essai prospectif sur les issues à long terme.

OBJECTIFS : Évaluer de manière prospective les prédicteurs de la NIC et les issues à long terme chez les patients touchés.

MÉTHODOLOGIE : Quatre cent douze patients consécutifs dont le taux de créatinine sérique oscillait entre 115 µmol/L et 309 µmol/L (1,3 mg/dL et 3,5 mg/dL) ayant subi une coronarographie non urgente ont participé à l'étude. Les patients étaient répartis au hasard entre l'hydratation péri-intervention, l'hydratation associée à une seule hémodialyse ou l'hydratation associée à de la *N*-acétylcystéine.

RÉSULTATS : Grâce à la régression logistique multivariée, les auteurs ont déposé que les éléments suivants sont des prédicteurs de NIC dans les 72 heures suivant l'intervention (équivalant à une augmentation d'au moins 44,2 µmol/L [0,5 mg/dL] de la créatinine) : hémodialyse prophylactique postintervention (RRR 2,86, 95 % IC 1,07 à 7,69), utilisation d'inhibiteurs de l'enzyme de conversion de l'angiotensine (RRR 6,16, 95 % IC 2,01 à 18,93); taux de filtration glomérulaire de départ (RRR 0,94, 95 % IC 0,90 à 0,98) et quantité d'agent de contraste (RRR 1,01, 95 % IC 1,00 à 1,01). Étant donné l'issue à long terme (suivi moyen de 649 jours), les modèles de régression de Cox multivariés ont révélé des taux de créatinine élevés à 30 jours (ratio de l'indice de risque [RIR] 5,48, 95 % IC 2,85 à 10,53), mais pas de NIC dans les 72 heures (RIR 1,12, 95 % IC 0,63 à 2,02), associés à une augmentation de la mortalité. De plus, les prédicteurs indépendants de décès pendant le suivi incluaient une fraction d'éjection ventriculaire gauche inférieure à 35 % (RIR 4,01, 95 % IC 2,22 à 7,26), du phosphate sérique (RIR 1,64, 95 % IC 1,10 à 2,43) et de l'hémoglobine (RIR 0,80, 95 % IC 0,67 à 0,96).

CONCLUSION : D'après le présent essai prospectif, l'effet de l'hémodialyse postintervention, le recours à des inhibiteurs de l'enzyme de conversion de l'angiotensine, le taux réduit de filtration glomérulaire de départ et la quantité d'agent de contraste étaient des prédicteurs indépendants de NIC dans les 72 heures suivant le cathétérisme. L'évaluation de la fonction rénale au bout de 30 jours, plutôt que de 72 heures, semblait être plus prédictive de la survie à long terme des patients.

The development of radiographic contrast media originated from the use of sodium iodide in radiography in 1918 (1), when Walter Dandy directly injected contrast media into the cerebral ventricles for visualizing the outline of the brain and the ventricular system. Since then, many different types of contrast media have been synthesized,

and many improvements in terms of side effects, such as hypersensitivity reactions, have been made. Moreover, associated acute renal failure, currently classified as contrast media-induced nephropathy (CIN), remains a major complication in hospitalized patients undergoing diagnostic or therapeutic interventional procedures using

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TABLE 1
Baseline patient characteristics and their association with contrast media-induced nephropathy (CIN) (creatinine increase of $\geq 44.2 \mu\text{mol/L}$ [0.5 mg/dL]) within 72 h after contrast media exposure

	All patients (n=412)	No CIN (n=374)	With CIN (n=38)	P
Age, years (mean $\pm$ SD)	67.1 $\pm$ 10.2	66.8 $\pm$ 10.4	70.5 $\pm$ 7.9	0.031
Women, n (%)	68 (16.5)	58 (15.5)	10 (26.3)	0.087
Diabetes, n (%)	121 (29.4)	104 (27.9)	17 (44.7)	0.03
Insulin-dependent	57 (13.8)	45 (12.7)	12 (32.4)	0.001
Number of diseased vessels, n (%)				
1	59 (14.3)	54 (15.7)	5 (13.5)	0.278
2	96 (23.3)	91 (26.4)	5 (13.5)	
3	159 (38.6)	139 (40.3)	20 (54.1)	
Ejection fraction $\leq 35\%$, n (%)	67 (16.2)	59 (15.8)	8 (11.9)	0.401
Creatinine, $\mu\text{mol/L}$ (mean $\pm$ SD)	141 $\pm$ 35	141 $\pm$ 35	159 $\pm$ 35	<0.001
(mg/dL)	1.6 $\pm$ 0.4	1.6 $\pm$ 0.4	1.8 $\pm$ 0.4	
Glomerular filtration rate, mL/min/1.73 m ² (mean $\pm$ SD)	47.1 $\pm$ 10.8	47.9 $\pm$ 10.5	39.0 $\pm$ 9.6	<0.001
Hemoglobin, g/L (mean $\pm$ SD)	136 $\pm$ 17	137 $\pm$ 17	127 $\pm$ 15	0.001
(g/dL)	13.6 $\pm$ 1.7	13.7 $\pm$ 1.7	12.7 $\pm$ 1.5	
Calcium, mmol/L (mean $\pm$ SD)	2.4 $\pm$ 0.1	2.4 $\pm$ 0.1	2.4 $\pm$ 0.1	0.96
Phosphate, mmol/L (mean $\pm$ SD)	3.4 $\pm$ 0.7	3.4 $\pm$ 0.7	3.66 $\pm$ 0.6	0.012
ACE inhibitors, n (%)	235 (57.0)	205 (55.0)	30 (78.9)	0.004
AT ₁ blockers, n (%)	36 (8.7)	33 (8.8)	3 (7.9)	0.843
Loop diuretics, n (%)	159 (38.6)	137 (36.7)	22 (57.9)	0.011
Other diuretics, n (%)	86 (20.9)	77 (20.6)	9 (10.5)	0.661
Contrast dye, mL (mean $\pm$ SD)	190 $\pm$ 80	187 $\pm$ 78	217 $\pm$ 92	0.024
Treatment strategy, n (%)				
Hydration only	139 (33.7)	129 (92.8)	10 (7.2)	0.002
Hydration plus hemodialysis	134 (32.6)	112 (83.6)	22 (16.4)	
Hydration plus N-ACC	139 (33.7)	133 (95.7)	6 (4.3)	

Differences between patients with and without CIN were analyzed by the ANOVA F-test for continuous variables and the χ^2 test for categorical variables. ACE Angiotensin-converting enzyme; AT₁ Angiotensin receptor 1; GFR Glomerular filtration rate; N-ACC N-acetylcysteine

contrast media. Previous studies (2-4) have shown that 3% to 37% of patients undergoing coronary angiography develop CIN. The incidence depended on the definition of CIN and the patient cohort studied. The development of CIN was associated with markedly poor in-hospital and long-term prognosis, with mortality rates found varying from 10% to 38% at one year in small, retrospective studies (2,5) to 81% at two years (6). There are currently an estimated 50 million procedures using iodinated contrast media performed worldwide each year (7), and radiographic contrast media are increasingly being used with recent progress in diagnostic noninvasive and invasive imaging techniques.

An increasing number of trials have addressed the prevention and confounding factors of CIN (2,4,6,8,9). However, there has been no prospective trial that provided data on the predictors of CIN and long-term survival of affected patients. For this reason, we evaluated the impact of different treatment strategies and baseline characteristics on the development of CIN and the long-term outcomes of patients in the Dialysis-Versus-Diuresis (DVD) trial (8), which is currently the largest randomized trial in this context, and the only one that prospectively assessed long-term survival.

METHODS

All patients who were admitted for elective left heart catheterization between January 1, 2001, and July 6, 2004, were screened for inclusion into the study. The major inclusion criterion was a serum creatinine value (determined using the Jaffe method [10]) of 115 $\mu\text{mol/L}$

(1.3 mg/dL) or more and 309 $\mu\text{mol/L}$ (3.5 mg/dL) or less. Exclusion criteria were acute or recent (within seven days) myocardial infarction, manifest heart failure (New York Heart Association class IV), reception of transplanted organs, monoclonal gammopathy and contrast dye exposition within seven days. The Ethical Committee of the Landesärztekammer Westfalen-Lippe and the Westfälische Wilhelms-University of Münster (Münster, Germany) approved the study protocol. Written informed consent was obtained from all patients enrolled in the study (8).

Baseline laboratory values and a medical history were obtained on admission. Patients were randomly assigned to receive one of the following treatments:

- hydration only (500 mL 5% glucose and 500 mL 0.9% sodium chloride over 12 h before and after heart catheterization);
- hydration plus hemodialysis (hemodialysis starting within 20 min after catheterization); or
- hydration plus N-acetylcysteine (N-ACC) (two oral doses of 600 mg N-ACC before and after catheterization).

Coronary angiography and percutaneous coronary intervention were performed using arterial access via the femoral or brachial artery. In the dialysis group, an arterial and venous sheath were placed for subsequent hemodialysis. Heart catheterization was performed with iopromide (Ultravist 370; Schering AG, Germany), a nonionic isosmolar contrast dye.

Definitions

For the purpose of the trial, renal function was determined based on serum creatinine measured enzymatically before administration of the contrast agent, and at 24 h, 48 h to 72 h and 30 days after catheterization. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease equation (11):

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 186 \times (\text{creatinine, mg/dL})^{-1.154} \times (\text{age, years})^{-0.203} \times 0.742 \text{ if female}$$

In accordance with other studies (1,3,4,9,12-17), CIN was defined as an increase in serum creatinine of 44.2 $\mu\text{mol/L}$ (0.5 mg/dL) or more within 72 h after the administration of the contrast agent. Creatinine levels at 30 days, which were 44.2 $\mu\text{mol/L}$ or more above the baseline creatinine level before heart catheterization, were classified as elevated creatinine levels at 30 days.

Long-term follow-up and censoring

A questionnaire assessing adverse events and repeated interventions was sent once to all patients. If the patients did not return their questionnaire (n=121), a follow-up telephone call was made to the patient, or a relative or the referring physician. The follow-up was conducted between September and October 2004. Patients were censored if they were still alive on September 1, 2004.

Statistics

Differences in basic clinical characteristics were tested by *t* test for continuous variables, and overall χ^2 test for dichotomous or categorical variables. P values for these tests are provided in the tables. Multivariate analyses of CIN were performed by binary logistic regression for the three treatments alone (crude OR) and after adjustment with potential covariates (adjusted OR). As covariates, parameters with $P < 0.1$ in the univariate analysis of CIN were chosen. Uni- and multivariate analyses of mortality during follow-up were analyzed by Cox regression models and calculation of hazard rate ratios (HRR) with 95% CI. For all tests, $P < 0.05$ was accepted to be significant.

RESULTS

Baseline characteristics of patients and treatment strategies, with respect to the development of CIN, are listed in Table 1. Patients

TABLE 2
Multivariate analysis by logistic regression with crude and adjusted OR for contrast media-induced nephropathy (CIN) within 72 h

	Patients, n (% of all)	CIN within 72 h, n (%)	Crude OR			Adjusted OR		
			OR	95% CI	P	OR	95% CI	P
Therapy								
Hydration only	139 (33.7)	10 (7.2)	1		0.003	1		0.006
Hydration plus dialysis	134 (32.6)	22 (16.4)	2.534	1.151–5.579		2.862	1.065–7.690	
Hydration plus <i>N</i> -acetylcysteine	139 (33.7)	6 (4.3)	0.582	0.206–1.648		0.565	0.164–1.950	
Covariates used for adjustment						OR	95% CI	P
Angiotensin-converting enzyme inhibitor use						6.161	2.005–18.934	0.002
Glomerular filtration rate						0.942	0.902–0.984	0.007
Amount of contrast dye						1.005	1.001–1.010	0.048
Diabetes						2.332	0.930–5.845	0.071
Phosphate						1.608	0.834–3.100	0.157
Hemoglobin						0.866	0.674–1.114	0.264
Sex						0.715	0.251–2.033	0.529
Age						1.012	0.965–1.060	0.624

All parameters found to be associated with renal failure within 72 h after catheterization in univariate analysis (Table 1) with $P < 0.1$ were included, except creatinine, because renal function was already entered into the model by the calculated* glomerular filtration rate. *Calculated by the Modification of Diet in Renal Disease formula

who developed CIN were older and suffered more often from diabetes. Furthermore, they had higher baseline serum creatinine and serum phosphate levels, and lower GFRs and hemoglobin values. In patients who developed CIN, the use of angiotensin-converting enzyme (ACE) inhibitors and loop diuretics was more frequent, and the amount of contrast dye used during catheterization was higher. However, the development of CIN neither correlated with the number of vessels diseased, nor did it occur more often in patients with severe left ventricular dysfunction (ejection fraction lower than 36%). With regard to the several treatment strategies, CIN within 72 h after contrast media exposure occurred more frequently in the hydration plus hemodialysis group (22 of 134 patients, 16.4%; $P = 0.002$) compared with the hydration plus *N*-ACC group (six of 139 patients, 4.3%) or the hydration only group (10 of 139 patients, 7.2%).

Multivariate analyses of CIN within 72 h

In a multivariate analysis, the partially overlapping influences of several factors were evaluated by logistic regression with crude and adjusted OR for CIN. All parameters that were found to be associated with CIN within 72 h after catheterization in univariate analysis (Table 1) with $P < 0.1$ were used for adjustment, except for creatinine, because renal function was already implemented by the calculated GFR, which is widely accepted as a more accurate measure of renal function.

These analyses showed that prophylactic hemodialysis significantly increased the risk for CIN, while the prophylactic administration of *N*-ACC had a slight but not significant positive effect compared with the hydration-only group (Table 2). Moreover, the use of ACE inhibitors in the preprocedural medical regimen, low baseline GFR, as well as the amount of contrast media used during catheterization, were independent predictors for the development of CIN within 72 h. In contrast, diabetes, high serum phosphate levels, low hemoglobin levels, the use of loop diuretics before catheterization and advanced age were not found to be independent predictors of CIN.

Predictors of elevated creatinine at 30 days after contrast media exposure

Patient characteristics at baseline and their association with elevated creatinine at 30 days after heart catheterization were analyzed by univariate tests (Table 3). Thus, diabetes, serum creatinine level, GFR, hemoglobin level, serum phosphate level, administration of

TABLE 3
Baseline patient characteristics and their association with elevated creatinine (creatinine increase of $\geq 44.2 \mu\text{mol/L}$ [0.5 mg/dL]) at 30 days after contrast media exposure

	All patients (n=372)	No CIN (n=353)	With CIN (n=19)	P
Age, years (mean $\pm$ SD)	66.81 $\pm$ 10.1	66.6 $\pm$ 10.2	70.2 $\pm$ 7.7	0.14
Women, n (%)	58 (15.6)	54 (15.3)	4 (21.1)	0.5
Diabetes, n (%)	109 (29.3)	99 (28.0)	10 (52.6)	0.022
Insulin-dependent	51 (13.7)	50 (14.2)	1 (5.3)	0.27
Number of diseased vessels, n (%)				
1	55 (16.0)	54 (16.5)	1 (5.9)	0.53
2	85 (24.7)	80 (24.5)	5 (29.4)	
3	143 (41.6)	134 (41.0)	9 (52.9)	
Ejection fraction $\leq 35\%$, n (%)	61 (16.4)	56 (15.9)	5 (8.2)	0.23
Creatinine, $\mu\text{mol/L}$ (mean $\pm$ SD)	141 $\pm$ 35	141 $\pm$ 35	150 $\pm$ 27	0.049
(mg/dL)	1.6 $\pm$ 0.4	1.6 $\pm$ 0.4	1.7 $\pm$ 0.3	
Glomerular filtration rate, mL/min/1.73 m ² (mean $\pm$ SD)	47 $\pm$ 11	48 $\pm$ 11	41 $\pm$ 11	0.008
Hemoglobin, g/L (mean $\pm$ SD)	137 $\pm$ 17	137 $\pm$ 17	128 $\pm$ 23	0.034
(g/dL)	13.7 $\pm$ 1.7	13.7 $\pm$ 1.7	12.8 $\pm$ 2.3	
Calcium, mmol/L (mean $\pm$ SD)	2.4 $\pm$ 0.1	2.5 $\pm$ 0.1	2.5 $\pm$ 0.1	0.26
Phosphate, mmol/L (mean $\pm$ SD)	3.4 $\pm$ 0.7	3.4 $\pm$ 0.7	3.8 $\pm$ 0.6	0.017
ACE inhibitors, n (%)	214 (57.5)	198 (56.1)	16 (84.2)	0.016
AT ₁ blockers, n (%)	33 (8.9)	32 (9.1)	1 (5.3)	0.56
Loop diuretics, n (%)	145 (39.1)	136 (38.6)	9 (47.4)	0.45
Other diuretics, n (%)	79 (21.3)	76 (21.6)	3 (15.8)	0.55
Contrast dye, mL (mean $\pm$ SD)	190 $\pm$ 80	190 $\pm$ 80	211 $\pm$ 92	0.245
Repeat heart catheterization, n (%)	156 (41.9)	150 (42.5)	6 (31.6)	0.35
CIN at 72 h, n (%)	62 (16.7)	55 (15.6)	7 (36.8)	0.015
Treatment strategy, n (%)				
Hydration only	127 (34.1)	119 (33.7)	8 (6.3)	0.68
Hydration plus hemodialysis	117 (31.5)	111 (31.4)	6 (5.1)	
Hydration plus <i>N</i> -ACC	128 (34.4)	123 (34.9)	5 (3.9)	

Differences between patients with and without elevated creatinine values at 30 days were analyzed by the ANOVA *F*-test for continuous variables and the χ^2 test for categorical variables. ACE Angiotensin-converting enzyme; AT₁ Angiotensin receptor 1; CIN Contrast media-induced nephropathy; *N*-ACC *N*-acetylcysteine

TABLE 4
Multivariate analyses of predictors associated with elevated creatinine at 30 days after contrast media exposure

Factor	OR	95% CI	P
CIN within 72 h	2.12	0.729–6.166	0.2
Hemoglobin	0.77	0.616–0.980	0.033
Angiotensin-converting enzyme inhibitors	3.417	0.984–11.866	0.053
Glomerular filtration rate	0.963	0.919–1.010	0.12
Diabetes	2.135	0.800–5.695	0.13
Phosphate	1.237	0.708–2.161	0.455

Predictors were analyzed by multivariate logistic regression models, with adjusted OR, 95% CI and P values given. CIN Contrast media-induced nephropathy

TABLE 5
Univariate analyses of long-term mortality using Cox regression models

Factor	Deaths, n (%)	HRR (95% CI)	P
Treatment strategy			
Hydration only	22 (15.8)	1	0.446
Hydration plus hemodialysis	27 (20.1)	1.41 (0.80–2.48)	
Hydration plus N-ACC	24 (17.3)	1.19 (0.61–1.94)	
Contrast media-induced nephropathy within 72 h			
No	64 (17.1)	1	0.691
Yes	9 (23.7)	1.12 (0.63–2.02)	
Increased creatinine ($\geq 44.2 \mu\text{mol/L}$ [0.5 mg/dL]) at 30 days			
No	54 (15.2)	1	<0.001
Yes	19 (56.3)	5.48 (2.85–10.53)	
Number of diseased vessels			
0	15 (22.1)	1	0.24
1	7 (11.5)	0.54 (0.19–1.49)	
2	17 (17.7)	0.99 (0.49–1.99)	
3	34 (21.4)	1.35 (0.73–2.48)	
Ejection fraction $\leq 35\%$			
No	49 (14.2)	1	<0.001
Yes	24 (35.8)	3.00 (1.84–4.90)	
Angiotensin-converting enzyme inhibitors			
No	23 (13.1)	1	0.035
Yes	50 (21.2)	1.70 (1.04–2.79)	
Glomerular filtration rate	–	0.97 (0.95–0.98)	<0.001
Amount of contrast dye	–	1.00 (1.00–1.00)	0.589
Diabetes			
No	44 (15.1)	1	0.009
Yes	29 (24.2)	1.874 (1.17–3.00)	
Phosphate	–	1.88 (1.38–2.57)	<0.001
Hemoglobin	–	0.79 (0.70–0.90)	<0.001
Sex			
Men	62 (18.0)	1	0.859
Women	11 (16.2)	1.06 (0.56–2.01)	
Age, years	–	1.03 (1.01–1.06)	0.021
Loop diuretics			
No	35 (13.9)	1	0.01
Yes	38 (23.3)	1.834 (1.16–2.91)	

The impact of different factors on long-term survival was analyzed by univariate Cox regression models, with hazard rate ratios (HRR), 95% CI and P values given. N-ACC N-acetylcysteine

ACE inhibitors and the occurrence of CIN at 72 h were significantly associated with increased creatinine values at 30 days. In contrast, age,

TABLE 6
Multivariate Cox regression models of predictors associated with long-term mortality

Factor	HRR	95% CI	P
Model A (including CIN at 72 h)			
CIN at 72 h	0.785	0.416–1.479	0.453
Ejection fraction $\leq 35\%$	3.908	2.255–6.773	<0.001
Phosphate	1.798	1.251–2.584	0.002
Hemoglobin	0.824	0.698–0.973	0.023
ACE inhibitors	1.636	0.946–2.829	0.078
Age	1.019	0.991–1.049	0.184
Diabetes	1.364	0.810–2.298	0.243
Glomerular filtration rate	0.993	0.969–1.018	0.597
Loop diuretics	1.059	0.621–1.807	0.833
Model B (including elevated creatinine at 30 days)			
Elevated creatinine at 30 days	2.899	1.360–6.178	0.006
Ejection fraction $\leq 35\%$	4.018	2.222–7.263	<0.001
Hemoglobin	0.801	0.672–0.955	0.014
Phosphate	1.638	1.102–2.434	0.015
Age	1.014	0.984–1.046	0.356
ACE inhibitors	1.266	0.701–2.287	0.434
Diabetes	1.242	0.700–2.206	0.459
Glomerular filtration rate	0.995	0.967–1.023	0.714
Loop diuretics	1.053	0.588–1.885	0.863

Factors associated with long-term mortality were analyzed by multivariate Cox regression models, with adjusted hazard rate ratios (HRR), 95% CI and P values given. ACE Angiotensin-converting enzyme; CIN Contrast media-induced nephropathy

left ventricular ejection fraction and repeat heart catheterization were not associated with elevated creatinine levels.

Multivariate analyses by logistic regression identified only hemoglobin levels as an independent predictor of elevated creatinine levels but not occurrence of CIN within 72 h (Table 4).

Long-term outcomes

The association of CIN and additional parameters with long-term mortality were also analyzed. The mean duration of the long-term follow-up in our trial was 649 days. Follow-up information about survival or death could be obtained from all patients. A total of 73 patients died during this period. Univariate Cox regression analysis was used to determine whether patients with increased serum creatinine ($44.2 \mu\text{mol/L}$ [0.5 mg/dL] or more) after 72 h or after 30 days were at higher risk for an unfavourable long-term outcome (Table 5). Thus, the occurrence of CIN within 72 h was not associated with an increased risk for death during follow-up, but increased creatinine levels at 30 days after catheterization were. Furthermore, low baseline GFR, diabetes, elevated phosphate levels, low hemoglobin concentrations, and the use of ACE inhibitors and loop diuretics were significantly associated with death during follow-up (Table 5).

By two different multivariate Cox regression models, potentially independent predictors of long-term mortality were assessed. First, the occurrence of CIN at 72 h together with the other significant predictors of long-term mortality (from Table 5) were used; thus, left ventricular ejection fraction lower than 36%, serum phosphate and hemoglobin levels were significant and independent predictors of long-term mortality, while CIN at 72 h was not (Table 6, model A). Second, a model including elevated creatinine levels at 30 days found this parameter, again together with the previous three, to be an independent predictor of long-term mortality (Table 6, model B).

Furthermore, cumulative survival was plotted from adjusted Cox regression models for the patients with or without CIN within 72 h (Figure 1, panel A), and for those who suffered or did not suffer from elevated serum creatinine levels at 30 days (Figure 1, panel B). These models again demonstrated that elevated creatinine levels at 30 days,

but not at 72 h, were predictive of long-term mortality of the patients in the present trial.

DISCUSSION

The hypothesis regarding whether one-time hemodialysis in combination with pre- and postprocedural hydration reduces the prevalence of CIN was tested in a randomized controlled trial. In brief, prophylactic hemodialysis appeared to be an ineffective and even harmful strategy for the prevention of CIN in patients with chronic kidney disease who are undergoing coronary angiography (8), as found by previous smaller studies (12,14,17).

Moreover, predictors of CIN and the impact of a contrast media-induced decrease in renal function on long-term mortality were prospectively assessed in our DVD trial. Presently, our study is the only prospective trial that provides data on the long-term outcome of patients with and without CIN. This is of considerable clinical relevance because the reported CIN-associated in-hospital and long-term mortality rates appear to be very high (2,3,5,6,15,16,18), while long-term data concerning this aspect are rare and have been derived only from small retrospective studies (2,3,5,6).

As mentioned above, some reports – all retrospective – showed that the in-hospital occurrence of CIN (usually determined within 72 h after catheterization) was associated with markedly higher in-hospital and long-term mortality. Interestingly, in contrast, our data consistently showed that persistently elevated creatinine values at 30 days after catheterization, and not the development of CIN within 72 h, had a significant effect on the long-term outcome of these patients. Our findings therefore raise the question of whether additional measuring of creatinine after four weeks may provide a better outcome measure, rather than assessing just serum creatinine within 72 h after contrast media application.

Predictors of CIN and long-term mortality

In previous studies, the role of ACE inhibitors in the development of CIN has been controversially discussed. Gupta et al (13) found a markedly preventive effect of treatment with captopril in patients with diabetes mellitus undergoing coronary angiography. They concluded that abnormalities of renal perfusion possibly mediated by the renin-angiotensin system are responsible for the development of contrast media-induced nephrotoxicity, and that ACE inhibitors may therefore offer protection against development of CIN (13). Dangas et al (16) reported that treatment with ACE inhibitors before percutaneous coronary intervention in patients with chronic kidney disease was associated with a lower risk of CIN. In contrast, Toprak et al (19) found that captopril was a risk factor for development of CIN. Maeder et al (9) concluded that in the presence of acute contrast media-induced reduction of renal blood flow, blunting of the vasoconstrictor effects of angiotensin II on the efferent arteriole may be deleterious due to a reduction of intraglomerular pressure. They therefore recommended the withdrawal of ACE inhibitors at least 24 h before contrast exposure (9). In our study, the use of ACE inhibitors was also an independent predictor for the development of CIN, but it was significantly correlated with an unfavourable long-term outcome. However, it remains unclear whether patients treated with ACE inhibitors have more comorbid factors (eg, pre-existing chronic heart failure) that can lead to complications or whether the ACE inhibitors themselves lead to complications when contrast media is used. The association of ACE inhibitors with adverse long-term outcomes is surely confounded by comorbidities, which represented the indication for the administration of ACE inhibitors. Therefore, more prospective studies are needed to better understand the role of ACE inhibitors in CIN.

CONCLUSION

Our data discourage the use of one-time hemodialysis in addition to periprocedural hydration. Furthermore, the development of CIN

Figure 1) Adjusted cumulative survival rates deriving from multivariate Cox regression models are shown for those patients who suffered from contrast media-induced nephropathy (CIN) within 72 h (A) and those with elevated creatinine levels at 30 days (B). Adjustment was made for age, baseline glomerular filtration rate, serum phosphate levels, hemoglobin levels, presence of diabetes, as well as administration of angiotensin-converting enzyme inhibitors and loop diuretics (see Table 5). Thus, there were no differences in survival, depending on the occurrence of CIN within 72 h (dotted line in A; $P=0.8$). In contrast, patients who suffered at 30 days from elevated creatinine levels showed markedly and significantly reduced survival (dotted line in B; $P=0.03$).

within 72 h did not have significant impacts on the long-term prognosis of affected patients, while an increased serum creatinine at 30 days turned out to be a strong predictor of long-term mortality. With regard to the use of ACE inhibitors in the preprocedural regimen, there is increasing evidence from the present and other studies that these drugs should be discontinued before contrast media administration because they were significantly associated with a higher rate of in-hospital CIN.

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