Clinical research

Does contrast media volume affect long-term survival in patients with chronic kidney disease?

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Submitted: 24 September 2017
Accepted: 10 October 2017

Arch Med Sci Atheroscler Dis 2017; 2: e82–e89
DOI: https://doi.org/10.5114/amsad.2017.71280

Abstract

Introduction: The aim of this study was to investigate the relationships between survival and related features in patients with chronic kidney disease undergoing cardiac catheterization and coronary angiography.
Material and methods: Three hundred and seven consecutive patients with an estimated glomerular filtration rate (e-GFR) less than 60 ml/min/1.73 m^2 undergoing coronary angiography were enrolled in the study. The study population was pursued with a median follow-up duration of 41.5 months.
Results: In the Cox proportional hazards regression model, age (HR = 1.047, 95% CI: 1.011–1.084, p = 0.01), contrast media volume (HR = 1.004, 95% CI: 1.001–1.007, p = 0.008), angiotensin II receptor blocker (ARB) use (HR = 0.485, 95% CI: 0.261–0.901, p = 0.02), and e-GFR (HR = 0.978, 95% CI: 0.940–1.016, p = 0.04) were found to be independent predictors of long-term all-cause mortality. The survival analysis showed that the long-term all-cause mortality rate was higher in patients using contrast media volume greater than 140 ml compared to patients given less than or equal to 140 ml during the coronary angiography (3.6% vs. 11.6% log-rank, p = 0.001).
Conclusions: In patients with chronic kidney disease undergoing cardiac catheterization, age, contrast media volume, e-GFR and low ARB use were found to be independent predictors of long-term all-cause mortality. Contrast media volume used > 140 ml was independently associated with long-term all-cause mortality compared to less than or equal to 140 ml during cardiac catheterization.

Key words: chronic kidney disease, mortality, coronary angiography, contrast media volume.

Introduction

Nowadays, cardiac catheterization has become an important tool in the treatment of cardiovascular disease (CVD). The risk of occurrence of a major complication (death, myocardial infarction, or major embolization) during diagnostic cardiac catheterization has become very rare. However, high-risk subgroups such as those aged above 60 years, women, those with New York Heart Association (NYHA) class IV heart failure, those with severe disease of the left main coronary artery and those with

a low left ventricular ejection fraction (LVEF) have been identified in multiple large series [1–4]. After cardiac catheterization, mortality is especially high in those with pre-existing renal insufficiency, especially those who experience further deterioration of renal function within 48 h of the procedure, particularly when dialysis is required [5]. Cardiovascular disease is the leading cause of morbidity and mortality among patients with end-stage renal disease [5], but cardiovascular risk is not limited to end-stage renal disease and, in fact, it begins well before its onset [6]. Hemmelgarn *et al.* demonstrated that in patients whose estimated glomerular filtration rate (e-GFR) was less than or equal to 79 ml/min/1.73 m^2, mortality after cardiac catheterization is elevated and e-GFR is a significant prognostic parameter in patients who have undergone cardiac catheterization [4]. However, no data exist on the prognostic markers in patients with an e-GFR of less than 60 ml/min/1.73 m^2 undergoing cardiac catheterization.

The aim of the present study was to investigate the predictors of all-cause mortality in patients with an e-GFR less than or equal to 60 ml/min/1.73 m^2 undergoing cardiac catheterization.

Material and methods

Patient population

This single-center prospective cohort study included 307 consecutive patients undergoing coronary angiography for suspected coronary artery disease (CAD) between 2010 and 2012. Inclusion criteria were patients older than 21 years of age and with an e-GFR less than 60 ml/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease formula. Exclusion criteria were as follows: (a) patients requiring dialysis and with an e-GFR less than 15 ml/min/1.73 m^2, (b) patients with uncontrolled hypertension (systolic and diastolic blood pressure greater than 160 and greater than 110 mm Hg, respectively), (c) exposure to radio-contrast agents within 7 days, (d) acute and chronic inflammatory disease, (e) medication with non-steroid anti-inflammatory drugs or metformin up to 2 days before entering the study, (f) pregnancy, (g) a known allergy to contrast agents and *n*-acetyl salicylic acid (NAC), and (h) patients receiving fenoldopam, mannitol, dopamine, and theophylline. Diuretics were withheld on the day of contrast injection. A non-ionic low osmolarity contrast medium called iopromide (Ultravist, 370 mg iodine/ml; Schering AG, Berlin, Germany) was used in all patients during the angiography procedure.

Measurements and definitions

Creatinine and blood urea nitrogen were measured the day before the administration of contrast media and 4, 24, and 48 h after administration. Serum creatinine was measured using the standard laboratory method. The Mehran risk score to estimate the risk of contrast induced nephropathy (CIN) was calculated for each case [7, 8]. Preprocedural creatinine clearance was calculated according to the Modification of Diet in Renal Disease formula [9]. The logistical clinical syntax score (log CSS) core model was calculated according to the formula developed by Farooq *et al.* [10]. The SYNTAX score was calculated using the criteria of the SYNTAX trial (defined as 50% or greater stenosis in any coronary vessel with a diameter of 1.5 mm or greater) [11]. The SYNTAX score was calculated retrospectively by 2 cardiologists blinded for the study patients. Two-dimensional and pulsed-wave Doppler echocardiography studies were performed with the patient in the left lateral decubitus position and using conventional views using a Vivid S6 device with a 3.5-MHz phased array transducer (GE Medical Systems, Horten, Norway) [12]. Left ventricular ejection fraction (LVEF) was calculated in all patients. The clinical endpoint of the research was all-cause mortality. All patients provided written informed consent. The study protocol was approved by the local Institutional Review Board and Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines.

Statistical analysis

All statistical calculations were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were presented as percentages. A χ^2 test was used for the comparison of categorical variables. The differences between normally and abnormally distributed numeric variables were evaluated using Student's *t*-test and the Mann-Whitney *U* test, respectively. Kaplan-Meier analysis was used to identify the cumulative incidence rates of long-term outcomes and the log-rank test was used to compare the groups. *P*-values of < 0.05 were considered significant. In addition, 95% confidence interval and odds ratios (OR) were presented together. The Cox proportional hazard regression model was created while investigating the influence of parameters on long-term all-cause mortality. Parameters having significance ($p < 0.05$) and parameters that were found to be significant in previous studies were included in the model. Hazard ratio (HR) values were expressed with 95% confidence intervals. The capacity of the contrast media volume in predicting the presence of mortality was analyzed using receiver operating characteristic (ROC) curve analyses.

Results

Baseline demographic, clinical, and angiographic characteristics of the patients are shown in Table 1, and baseline laboratory characteristics of the patients are presented in Table 2. Three hundred and seven patients were included in the analysis, median age of the patients was 67 (min. 39, max. 82), median nody mass index (BMI) of the patients was 27.8 kg/m^2 (min. 18, max. 43.3), and 63.4% (n = 195) of the study subjects were male. Sixty-three of the patients (20.5%) died during the median follow-up of 41.5 months (1–54 months).

Table I. Baseline clinical characteristics and procedural details of the study population

Variables	Survivors (n = 244)	Non-survivors (n = 63)	P-value
Age, mean ± SD [years]	65.1 ±8.7	69.2 ±7.3	0.001
Male gender, n (%)	155 (63.5)	40 (63.5)	1
Body mass index [kg/m^2]	28.9 ±4.6	27.1 ±4.0	0.008
Hypertension, n (%)	208 (85.2)	47 (74.6)	0.045
Systolic blood pressure [mm Hg]	134.7 ±16.2	137 ±15.8	0.342
Diastolic blood pressure [mm Hg]	76.6 ±9.3	74.7 ±10	0.152
Diabetes mellitus, n (%)	126 (51.6)	28 (44.4)	0.309
CAD history, n (%)	135 (55.3)	35 (55.6)	0.974
Congestive heart failure, n (%)	18 (7.4)	7 (11.1)	0.334
Stroke history, n (%)	14 (5.7)	8 (12.7)	0.056
Peripheral arterial disease, n (%)	31 (12.7)	15 (23.8)	0.028
Current smoking, n (%)	110 (45.1)	30 (47.6)	0.719
Medications, n (%):			
ACEI use	95 (38.9)	25 (39.7)	0.914
ARB use	92 (37.7)	14 (22.2)	0.021
Statins use	96 (39.3)	17 (27)	0.070
Diuretics use	82 (33.6)	29 (46)	0.067
β-Blockers use	150 (61.5)	38 (60.3)	0.866
Calcium channel blockers use	74 (30.3)	17 (27)	0.604
N-acetyl cysteine use	158 (64.8)	46 (73)	0.216
Angiography, n (%):			0.279
No lesion	17 (7)	2 (3.2)	
Non-critical lesion	50 (20.5)	8 (12.7)	
One coronary occluded	47 (19.3)	10 (15.9)	
Two coronaries occluded	54 (22.1)	18 (28.6)	
> 2 coronaries occluded	76 (31.1)	25 (39.7)	
Volume of contrast media ≥ 140 ml	69 (28.3)	33 (52.4)	< 0.001
Contrast induced nephropathy	26 (10.7)	8 (12.7)	0.645
Nephropathy class, n (%):			0.492
e-GFR [ml/min/1.73 m^2] (59–30)	227 (93)	57 (90.5)	
e-GFR [ml/min/1.73 m^2] (15–29)	17 (7)	6 (9.5)	

CAD – coronary artery disease, ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, e-GFR – estimated glomerular filtration rate.

Table II. Comparisons of baseline laboratory results and other measurements among groups

Variables	Survivors (n = 244)	Non-survivors (n = 63)	P-value
Hematocrit level (%)	38.1 ±5.1	37.1 ±5.7	0.179
White blood cell count [× 10^9/l]	7.5 ±1.8	8.5 ±2.5	0.192
Neutrophil count [× 10^9/l]	4.8 ±1.5	5.5 ±2.2	0.011
Lymphocyte count [× 10^9/l]	2.0 ±0.6	2.5 ±0.2	0.957
Platelet count [× 10^9/l]	231.1 ±58.1	245.5 ±92.1	0.665
Neutrophil-to-lymphocyte ratio	2.7 ±1.3	3.5 ±2.1	0.001
Platelet-to-lymphocyte ratio	129.1 ±50.1	152.5 ±75.2	0.012
Fasting glucose [mg/dl]	136 ±65	124 ±48	0.640
Baseline blood urea nitrogen [mg/dl]	26.1 ±8.1	29.7 ±9.6	0.006
Baseline serum creatinine [mg/dl]	1.5 ±0.3	1.6 ±0.4	0.100
Uric acid [mg/dl]	6.8 ±1.6	7.3 ±1.7	0.031
Triglycerides [mg/dl]	193.0 ±117.4	153.8 ±95.6	0.001
Total cholesterol [mg/dl]	191.1 ±47.6	181.2 ±49.9	0.148
LDL-C [mg/dl]	118.3 ±40.1	113.8 ±39.3	0.429
HDL-C [mg/dl]	40.8 ±11.3	41.2 ±11.9	0.912
hs-CRP [mg/dl]	4.9 ±3.5	6.3 ±4.1	0.007
LVEF (%)	53 ±10	52 ±11	0.427
LVEF < 40, n (%)	21 (8.6)	10 (15.9)	0.088
Baseline e-GFR [ml/min/1.73 m^2]	45.5 ±8.9	42.7 ±9.9	0.041
Procedure time [min]	22 ±16	31 ±20	< 0.001
Contrast media volume [ml]	116 ±67	158 ±89	< 0.001
Mehran risk score	7.6 ±3.2	8.7 ±3.1	0.017
Log CSS	8.9 ±2.8	9.7 ±3.1	0.049

Values are presented as mean ± SD. hs-CRP – high-sensitivity C-reactive protein, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, e-GFR – estimated glomerular filtration rate, LVEF – left ventricular ejection fraction, Log CSS – Logistic Clinical Syntax Score.

The non-survivors were elderly (69.2 ±7.3 vs. 65.1 ±8.7, p = 0.001) and the prevalence of peripheral arterial disease (PAD) was higher among the non-survivors (23.8% vs. 12.7%, p = 0.02). Body mass index was lower among the non-survivors (p = 0.008). The prevalence of hypertension and angiotensin II receptor blocker (ARB) use were higher among the survivors than the non-survivors (p = 0.04 and p = 0.02, respectively). The MEHRAN score and log CSS were higher among the non-survivors (8.7 ±3.1 vs. 7.6 ±3.2; p = 0.01; 9.7 ±3.1 vs. 8.9 ±2.8; p = 0.04, respectively). Estimated GFR was lower among the non-survivors (42.7 ±9.9 vs. 45.5 ±8.9; p = 0.04), and there was no difference between the two groups in terms of the occurrence of CIN after cardiac catheterization. The levels of hs-CRP were higher among the non-survivors than the survivors (p = 0.007). The neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio were higher among the non-survivors than the survivors (p = 0.001 and p = 0.01, respectively). In terms of angiographic procedure, the amount of contrast media volume was significantly higher among the non-survivors (158.0 ±89.2 vs. 116.3 ±67.5, p < 0.001) and the duration of the procedure was longer in the non-survivors than the survivors (31.3 ±20.3 vs. 22.4 ±16.1; p < 0.001). A receiver operating characteristics (ROC) curve was generated to investigate the predictive value of the contrast media volume for mortality in patients undergoing coronary angiography. It was found that a contrast media volume of greater than 140 ml had 52.4% sensitivity and 71.7% specificity in the prediction of mortality among the patients (AUC = 0.656, 95% CI: 0.581–0.731; p < 0.001) (Figure 1). The

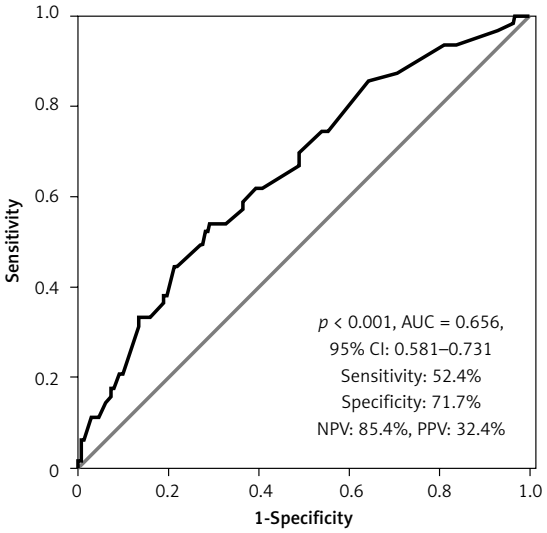

Figure 1. ROC analyses of the amount of contrast media for predicting total mortality

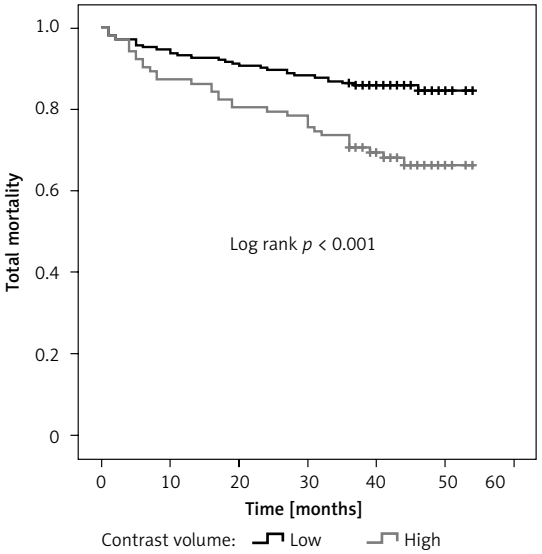

Figure 2. Kaplan-Meier analyses for long-term all-cause mortality rate according to the amount of contrast media

median follow-up duration was 41.5 months (1–54 months). The rate of long-term all-cause mortality was 20.5% in the overall patient group. The survival analysis showed that the long-term all-cause mortality rate was higher among patients given greater than 140 ml of contrast media volume compared to patients given less than or equal to 140 ml during the procedure (3.6% vs. 11.6% log-rank, $p = 0.001$) (Figure 2). Univariate analyses showed that age, BMI, e-GFR, hypertension (HT), log CSS, PAD, uric acid, hs-CRP and the amount of contrast media volume differed significantly between the survivors and non-survivors (Table 3). In the Cox proportional hazards regres-

Table III. Factors predicting total mortality on univariate COX regression analysis

Variables	*P*-value	HR	95% CI
Hypertension	0.042	0.554	0.314–0.978
Age	0.001	1.055	1.022–1.090
Hs-CRP	0.005	1.103	1.030–1.181
Body mass index	0.011	0.924	0.870–0.982
Peripheral arterial disease	0.028	1.919	1.074–3.428
ARBs use	0.029	0.516	0.285–0.934
Statins use	0.075	0.603	0.346–1.053
LVEF	0.228	0.986	0.963–1.009
Volume of contrast media	< 0.001	1.005	1.003–1.008
Contrast induced nephropathy	0.656	1.184	0.564–2.485
Uric acid	0.042	1.158	1.006–1.334
e-GFR	0.028	0.973	0.949–0.997
N-acetyl cysteine use	0.226	1.410	0.808–2.460
Neutrophil/lymphocyte ratio	< 0.001	1.224	1.108–1.353
Platelet/lymphocyte ratio	0.002	1.005	1.002–1.009
Log CSS	0.053	1.083	0.999–1.174

HR – hazard ratio, CI – confidence interval, hs-CRP – high-sensitivity C-reactive protein, ARB – angiotensin receptor blocker, LVEF – left ventricular ejection fraction, e-GFR – estimated glomerular filtration rate, Log CSS – logistic clinical Syntax score.

Table IV. Factors predicting total mortality on multivariate COX regression analysis

Variables	*P*-value	HR	95% CI
e-GFR	0.04	0.972	0.946–0.999
Uric acid [mg/dl]	0.127	1.134	0.965–1.332
Volume of contrast media [ml]	0.002	1.005	1.002–1.008
Statin use	0.98	0.617	0.347–1.094
ARB use	0.015	0.458	0.244–0.858
Peripheral arterial disease	0.973	0.989	0.516–1.894
Hypertension	0.43	0.785	0.427–1.444
Body mass index	0.265	0.964	0.905–1.028
Age	0.002	1.054	1.019–1.091
hs-CRP	0.062	1.070	0.997–1.150
Log CSS	0.526	1.029	0.942–1.124

HR – hazard ratio, CI – confidence interval, e-GFR – estimated glomerular filtration rate, ARB – angiotensin receptor blocker, hs-CRP – high-sensitivity C-reactive protein, Log CSS – logistic clinical Syntax score.

sion model, age (HR = 1.054, 95% CI: 1.019–1.091, p = 0.002), contrast media volume (HR = 1.005, 95% CI: 1.002–1.008, p = 0.002), ARB use (HR = 0.458, 95% CI: 0.244–0.858, p = 0.01), and e-GFR (HR = 0.972, 95% CI: 0.946–0.999, p = 0.04) were found to be independent predictors of long-term all-cause mortality (Table 4).

Discussion

The present study revealed that contrast media volume was the strongest predictor of mortality in patients undergoing cardiac catheterization with an e-GFR of less than or equal to 60 ml/min/1.73 m^2, and it was irrespective of CIN development. In this study, the other predictors of all-cause mortality were age, e-GFR and low ARB use.

Cardiovascular disease is known as a significant cause of mortality in patients with chronic kidney disease in which subclinical atherosclerosis has already begun before end-stage kidney disease [6, 13]. Pre-existing subclinical atherosclerosis could potentially account for the observed increase in CVD mortality in patients with renal failure. Beddhu *et al.* [6] demonstrated the relation with baseline e-GFR and death. Despite the increased complication rate among patients with renal failure, coronary angiography remains a gold standard diagnostic tool in the diagnosis of CAD. Hemmelgarn *et al.* investigated the impact of renal insufficiency on survival after coronary angiography, and renal insufficiency was found to be an independent predictor of mortality after coronary angiography in both dialysis-dependent and -independent patients [13]. In another study, Hemmelgarn *et al.* [4] demonstrated an increased risk of death in patients with an e-GFR of less than 79 ml/min/1.73 m^2. The complications of renal failure such as anemia and deterioration of calcium phosphate metabolism increase with an e-GFR of less than 60 ml/min/1.73 m^2 [14, 15]. In the present study, the aim was to assess the predictors of all-cause mortality in patients with an e-GFR of less than 60 ml/min/1.73 m^2. In the present study, as with previous studies, e-GFR was found to be an independent predictor of all-cause mortality. The strongest predictor of total mortality that was found in this study is the amount of contrast media. The amount of contrast media used in a coronary angiography procedure is one of the most important causes of CIN, which is related to high mortality and morbidity rates [16–18]. The most important predictors of CIN are e-GFR and contrast media volume. In the present study, there was no difference between survivors and non-survivors in terms of the development of CIN. However, independent of the development of CIN, the amount of contrast media was found to be a predictor of mortality in patients with an e-GFR of less than 60 ml/min/1.73 m^2 who underwent coronary angiography. In the Kaplan-Meier analysis, a contrast volume of greater than 140 ml was found to be related to mortality. It is known that contrast agents have hyper-osmotic compounds and they contact endothelial cells. Contrast media injections directly affect the endothelium and inhibit nitric oxide (NO) production, and they lead to deterioration of the shear stress-induced stimulation of NO production [19]. The endothelium regulates vascular tone by releasing NO, the endothelium-derived hyperpolarizing factor prostacyclin, or natriuretic peptides. Furthermore, these mediators prohibit thrombus formation and vascular stenosis via anti-aggregator properties. In addition, the en-

dothelium acts synergistically with a regulatory system, which consists of vasoconstrictors such as catecholamines and other vasoactive peptides (i.e., angiotensin, vasopressin, and endothelin) [20]. The deterioration of this regulatory system by exposure to contrast media may be one of the reasons for the relation between contrast media volume and mortality that was found in this study. Contrast media injections also cause changes to intracellular PH, mitochondrial dysfunction, and apoptosis [19–22]. Zhang *et al.* demonstrated that radiographic contrast media are related to reduced proliferation and increased apoptosis of human vascular endothelial cells, and they considered that this relation may be dependent on the osmolality of the contrast media and the chemical structure of these agents [19]. Then, irrespective of the development of CIN, increased mortality with the use of a high volume of contrast media may be due to endothelial injury. The log CSS, a combined risk score, developed by Farooq *et al.* [10], includes patient's clinical (age, LVEF, and creatinine clearance) and anatomical (SYNTAX score) parameters. The log CSS was calculated in the present study to evaluate the complexity of coronary artery disease and fragility of patients. It was found higher in the non-survivors than survivors but was not found to be a predictor of mortality in the multivariate analysis. However, high volume of contrast media was found to be a predictor of mortality regardless of the complexity of coronary artery disease and fragility of patients.

The activity of the renin-angiotensin-aldosterone system (RAAS) is elevated both in the circulation and in the renal tissue of diabetic and non-diabetic nephropathies [23]. The increased RAAS activity plays an important role in the hemodynamic and non-hemodynamic pathogenetic mechanisms involved in chronic kidney disease [23]. Randomized crossover and parallel blind studies in patients with diabetic nephropathy have demonstrated that angiotensin-converting enzyme (ACE) inhibition and ARBs induce favorable changes in systemic blood pressure, renal hemodynamics and proteinuria [23–26]. These medications have been shown to preserve kidney function by slightly reducing the filtration rate in the kidneys. Similarly, in this study, lower use of ARBs was found to be a predictor of all-cause mortality in patients with an e-GFR of less than 60 ml/min/1.73 m^2 who underwent coronary angiography. This study does have some limitations. The main limitations of our study were that it was single centered and had a small patient population size. We were not able to establish clear and detailed causes of mortality such as cardiovascular or others, so we used all-cause mortality in the analyses. In relation to the amount of contrast media given during cardiac catheterization, long-term survival has not been studied adequately to date. Despite the limitations, the importance of the present study results from the fact that it reveals the relation between contrast media volume and long-term mortality in this patient group.

In conclusion, in patients with chronic kidney disease undergoing cardiac catheterization, age, contrast media volume, e-GFR and low ARB use were found to be independent predictors of long-term all-cause mortality. Contrast media volume used > 140 ml was independently associated with long-term all-cause mortality compared to less than or equal to 140 ml during cardiac catheterization. Reducing the volume of contrast agent used could contribute significantly to the reduction in long-term mortality in patients with chronic kidney disease.

Conflict of interest

The authors declare no conflict of interest.

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