

Age-related effect of trimetazidine in the prevention of contrast-induced nephropathy in patients with preserved renal function

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ABSTRACT

Objectives: This study aims to investigate whether trimetazidine (TMZ) alone has a preventive effect on contrast-induced nephropathy (CIN) in patients with preserved kidney function who underwent angiographic procedures and the variables associated with CIN development.

Patients and methods: Between June 2023 and September 2023, a total of 305 patients (199 males, 106 females; mean age: 60±10 years; range, 54 to 67 years) who underwent coronary angiographic procedures with diagnosed or suspected stable coronary artery disease and an estimated glomerular filtration rate (eGFR) of >60 mL/min/1.73 m² were included. A total of 153 patients received TMZ (TMZ group), while 152 patients were naïve to TMZ (non-TMZ group).

Results: Ten patients (6.5%) in the non-TMZ group and nine patients (5.8%) in the TMZ group developed CIN within 48 to 72 h (p=0.801) after the procedures. The mean serum creatinine level increased from 0.84±0.1 mg/dL to 0.89±0.2 mg/dL in the non-TMZ group (p<0.001) and from 0.84±0.1 mg/dL to 0.88±0.2 mg/dL in the TMZ group (p=0.008). Multivariate logistic regression analysis revealed that only age (odds ratio [OR]: 1.10, 95% CI: 1.03-1.18, p=0.003) was an independent predictor of CIN. A cut-off value of 60 years (area under the curve [AUC]=0.785; sensitivity, 100%; specificity, 52%) predicted CIN development in the non-TMZ group, whereas it was 72.5 years (AUC=0.711; sensitivity, 55%; specificity, 90%) for the TMZ group.

Conclusion: Our study results suggest that the use of TMZ may be beneficial on CIN in elderly patients undergoing coronary angiographic procedures, even if the eGFR is ≥60 mL/min/1.73 m².

Keywords: Age, contrast-induced acute kidney injury, contrast-induced nephropathy, coronary angiography, percutaneous coronary intervention, trimetazidine.

Contrast-induced nephropathy (CIN) is a serious complication of angiographic procedures, resulting from the administration of iodinated contrast media (CM).^[1] It is the third most common cause of acute kidney injury in patients requiring hospitalization and is associated with a consequent worsening clinical outcome.^[2,3] Among all procedures using CM for diagnostic or therapeutic purposes, coronary angiography (CAG) and percutaneous coronary interventions (PCIs) are associated with the highest rates of CIN.^[2]

Various variables on CIN have been identified, and the Mehran risk score for the prediction of CIN development was defined.^[4] Pre-existing kidney disease with high serum creatinine level is the

most important risk factor for the development of CIN. Various studies have shown that an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m² is a reliable cut-off point for identifying patients at high risk for developing CIN. Several studies have provided evidence

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that advanced age is an independent predictor of CIN.^[5] In particular, individuals over the age of 70 are considered at risk for CIN.^[6,7]

Currently, intravenous (IV) fluid hydration therapy is the only widely accepted treatment to prevent the disease. Since no additional pharmaceuticals have been proven to effectively treat CIN, preventing its development is of critical importance. Trimetazidine (TMZ) is one of the drugs currently being studied for the prevention of CIN. It has traditionally been used as an anti-ischemic drug for coronary artery disease (CAD) by selectively inhibiting mitochondrial long-chain 3-ketoacyl-CoA thiolase and appears to have a hemodynamically neutral side-effect profile.^[8,9]

In the present study, we aimed to investigate the protective effect of TMZ alone on CIN in patients with diagnosed or suspected stable CAD (SCAD) and preserved kidney function who underwent angiographic procedures and the variables associated with CIN development.

PATIENTS AND METHODS

This single-center, prospective, observational study was conducted at Katip Çelebi University Atatürk Training and Research Hospital, Department of Cardiology between June 1st, 2023 and September 30th, 2023. Patients with eGFR >60 mL/min/1.73 m², older than 18 years of age, diagnosed or suspected SCAD, and CAG indications were included in the study. Patients who regularly used 35 mg of TMZ dihydrochloride twice a day for the last 48 h and continued treatment for at least 48 to 72 h after the procedure (initiated and/or started by a cardiologist), and patients who did not use TMZ before and after the procedure were compared in terms of the frequency of development of CIN. Those with baseline renal failure (eGFR <60 mL/min/1.73 m²), patients under 18 years of age, pregnant and lactating women, hypotensive patients, patients who received contrast material in the last two weeks, patients who took non-steroidal anti-inflammatory drugs or nephrotoxic antibiotics within the past seven days, patients who received intensive IV hydration, patients who used N-acetylcysteine or antioxidant agents and patients under ranolazine treatment were excluded from the study. The drugs mostly

eliminated by the kidney, such as metformin and angiotensin enzyme inhibitors or receptor blockers, were not discontinued before the procedure. A total of 305 patients (199 males, 106 females; mean age: 60±10 years; range, 54 to 67 years) were included in the study. Written informed consent was obtained from each patient. The study protocol was approved by the İzmir Katip Çelebi University Clinical Research Ethics Committee (Date: 10.03.2022, No: 28). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

Case report forms were filled in prospectively with patient data registered in the Hospital Information Management System, patient files, and information obtained through face-to-face interviews. Demographic characteristics, history, presence of chronic diseases, physical examinations, laboratory tests, imaging tests, and medications used by the patients were recorded.

Peripheral venous blood samples of the patients were obtained at baseline (within 24 h before the procedure) and 48 to 72 h after the procedure. Pre-procedure eGFR, creatinine, and blood urea nitrogen (BUN) levels, biochemical parameters, complete blood count, and post-procedure creatinine and BUN levels of patients were recorded. Anemia was defined as a hemoglobin concentration less than 13 g/dL in men and 12 g/dL in women. An eGFR was calculated according to the Modification of Diet in Renal Disease (MDRD) equation.^[9]

Interventional procedures were evaluated in three groups: (i) CAG; (ii) PCI with/without CAG; (iii) CAG and other angiography procedures (carotid angiography, peripheral angiography, aortography, ventriculography). Angiographic procedures were performed by experienced cardiologists via standard techniques, who were blinded to details of the study. A low-osmolar, non-ionic, monomeric contrast agent, iohexol (350 mg of iodine per mL; 780 mOsm per kg of water [Omnipaque, Amersham Health, GE Healthcare Cork, Ireland]) was used in all patients. The amount of CM was recorded. The Mehran score was used to estimate CIN development risk.^[9] Contrast-induced nephropathy was defined as an increase in creatinine of ≥25% or ≥0.5 mg/dL within 48 to 72 h after contrast material administration if other predisposing factors for renal injury did not occur.^[10]

Table 1
Comparisons of baseline characteristics between the non-TMZ group and the TMZ group

	Non-TMZ group (n=152)				TMZ group (n=153)				p		
	n	%	Mean±SD	IQR	Q1-Q3	n	%	Mean±SD		IQR	Q1-Q3
Clinical characteristics											
Age (year)			59.7±11.0					61.2±9.22		0.172	
Sex											
Male	101	66.4				98	64.0			0.750	
BMI (kg/m ²)			28.63±5.19					29.52±4.80		0.135	
Diabetes mellitus	61	40.1				59				0.870	
Hypertension	91	59.9				106				0.110	
Dyslipidemia	98	64.5				111				0.163	
Anemia	38	25.0				34	22.2			0.568	
Current smoking	44	28.9				59				0.098	
LVEF (%)			56.90±8.38					56.56±6.92		0.395	
Laboratory findings											
Fasting blood glucose (mg/dL)				106	97.0-129				106	96.0-122	0.862
Baseline serum creatinine (mg/dL)				0.82	0.74-0.92				0.82	0.74-0.93	0.830
Baseline eGFR (mL/min/1.73 m ²)				89.8	75.7-102				88.0	77.0-99.0	0.437
Hemoglobin (g/dL)			13.7±1.68					13.7±1.69			0.862
Total cholesterol (mg/dL)				190	166-230				190	160-221	0.870
LDL cholesterol (mg/dL)			121±40.6					117±40.9			0.417
HDL cholesterol (mg/dL)				43.0	36.0-50.0				40.0	33.0-48.0	0.038
Triglyceride (mg/dL)				139	95.0-180				161	108-214	0.008
In Hospital Medication											
Insulin	24	15.8				25	16.3				1.000
Metformin	18	11.8				15	9.80				0.698
Other oral antidiabetic	18	11.8				20	13.1				0.879
ACEi - ARB	82	53.9				84	54.9				0.958
Diuretic	33	21.7				44	28.8				0.199
Statin	72	47.4				82	53.6				0.331
Beta blocker	80	52.6				109	71.2				0.001
Calcium channel blocker	17	11.2				30	19.6				0.060
Nitrate	23	15.1				47	30.7				0.002

SD: Standard deviation; IQR: Interquartile range; Q₂: Quartile; BMI: Body mass index; LVEF: Left ventricular ejection fraction; eGFR: Estimated glomerular filtration rate; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker.

SD: Standard deviation; IQR: Interquartile range; Q: Quartile; BMI: Body mass index; LVEF: Left ventricular ejection fraction; eGFR: Estimated glomerular filtration rate; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker.

The modified Simpson's method (biplane disc method) was used for left ventricular ejection fraction (LVEF) measurement with the EPIQ 7C unit (Philips Medical Imaging, Eindhoven, Netherlands) as recommended by the European Association of Cardiovascular Imaging (EACVI).^[11]

Statistical analysis

Based on previous studies, the incidence of contrast-induced nephropathy was estimated to be 5-10%. Accordingly, the study calculated a minimum sample size of 300 patients to achieve 80% power with a 0.05 margin of error.

Statistical analysis was performed using the IBM SPSS version 24.0 software (IBM Corp., Armonk, NY, USA). Compliance of numerical data with normal distribution was evaluated using the Kolmogorov-Smirnov tests. Continuous data were expressed in mean $\pm$ standard deviation (SD) or median (Q1-Q3), while categorical data were expressed in number and frequency. The Mann-Whitney U test was used to compare numerical variables between two independent groups, and the Wilcoxon test was used to compare two dependent groups. The chi-square test was used to compare categorical variables. Multivariate logistic regression analysis was used to explore possible predictors of CIN. Receiver operating characteristic (ROC) curve analysis values were presented to evaluate the effect

of age on the CIN occurrence in patients using and not using TMZ. A p value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

The TMZ and non-TMZ groups had similar baseline characteristics: age, sex, body mass index (BMI), underlying disease, LVEF, eGFR, serum creatinine, and hemoglobin levels (Table 1). Patients in the TMZ group were more frequently ordered to receive beta-blocker (71.2% *vs.* 52.6%; $p<0.001$) or nitrate therapies (30.7% *vs.* 15.1%; $p<0.002$). While 19.6% of the patients in the TMZ group were taking calcium channel blockers, 11.2% of the patients in the non-TMZ group were taking calcium channel blockers ($p=0.06$).

Table 2 shows the comparison of angiographic procedure characteristics between the non-TMZ and TMZ groups. There were no significant differences between the two groups in terms of angiographic procedure type, amount of contrast volume used during these procedures, and the distribution of the Mehran score. Ten patients (6.5%) in the non-TMZ group and nine patients (5.8%) in the TMZ group developed CIN within 48 to 72 h ($p=0.801$) after the procedures.

Table 2
Comparison of angiographic procedure characteristics between the non-TMZ group and the TMZ group

	Non-TMZ group (n=152)				TMZ group (n=153)				<i>p</i>
	n	%	IQR	Q1-Q3	n	%	IQR	Q1-Q3	
Angiographic procedures									
CAG	52	34.2			61	39.9			0.574
PCI + angiographic procedures	46	30.3			44	28.8			
CAG + other angiographic procedures	54	35.5			48	31.4			
Contrast volume (mL)			70.0	50.0-180			80.0	50.0-150	0.628
Mehran score			3.00	0.00-4.25			3.00	0.00-4.00	
Categorical of Mehran score									
Low	127	83.6			128	83.7			0.801
Moderate	25	16.4			24	15.7			
High	0	0.00			1	0.65			
CIN	10	6.6			9	5.9			

IQR: Interquartile range; Q: Quartile; CAG: Coronary angiography; PCI: Percutaneous coronary intervention; CIN: Contrast-induced nephropathy.

Table 3			
Serum creatinine and BUN changes between baseline and 48-72 h after invasive procedures in groups			
	Baseline	48-72 hours	
	Mean±SD	Mean±SD	<i>p</i>
Non-TMZ group			
Creatinine (mg/dL)	0.84±0.1	0.89±0.2	<0.001
BUN (mmol/L)	16.0±4.6	16.3±4.9	0.297
TMZ group			
Creatinine (mg/dL)	0.84±0.1	0.88±0.2	0.008
BUN (mmol/L)	15.1±4.1	16.0±3.0	0.299

BUN: Blood urea nitrogen; SD: Standard deviation; TMZ: Trimetazidine group.

Table 3 summarizes serum creatinine and BUN level changes between baseline and 48 to 72 h after invasive procedures. The mean serum creatinine level increased from 0.84±0.1 mg/dL to 0.89±0.2 mg/dL ($p<0.001$) in the non-TMZ group and from 0.84±0.1 mg/dL to 0.88±0.2 mg/dL ($p=0.008$) in the TMZ group.

Table 4			
Predictors of contrast-induced nephropathy by multivariate logistic analysis			
	OR	95% CI	<i>p</i>
Age	1.10	1.03-1.18	0.003
Sex (male)	2.42	0.58-10.10	0.225
Trimetazidine	0.93	0.31-2.74	0.899
Diabetes mellitus	1.49	0.50-4.42	0.464
Dislipidemia	0.79	0.23-2.71	0.710
Current smoking	1.15	0.35-3.74	0.813
Contrast volume	1.00	0.99-1.01	0.225
Anemia	0.62	0.17-2.49	0.473
LVEF	3.69	0.72-18.94	0.117
eGFR	0.99	0.96-1.03	0.96
ACEi - ARB	1.67	0.46-5.94	0.429
Nitrate	0.52	0.12-2.20	0.379
Diuretic	1.30	0.38-4.42	0.672
Beta blocker	0.61	0.20-1.91	0.405
Statine	2.18	0.67-7.04	0.192

OR: Odds ratio; CI: Confidence interval; LVEF: Left ventricular ejection fraction; eGFR: Estimated glomerular filtration rate; ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker.

Multivariate analysis of variables, including clinical features, medical history, amount of contrast used, medications, and blood parameters thought to be related to CIN, is presented in Table 4. Multivariate analysis revealed that only age (odds ratio [OR]: 1.10, 95% CI: 1.03-1.18, $p=0.003$) was an independent predictor of CIN. The ROC analysis was performed to identify the most optimal cut-off values for age as a predictor of CIN development. A cut-off value of 60 years (area under the curve [AUC]=0.785; sensitivity 100%, specificity 52%) predicted CIN development in patients naïve to TMZ use, while it was 72.5 years (AUC=0.711; sensitivity 55%, specificity 90%) for patients receiving TMZ (Figure 1).

DISCUSSION

In the current study, we investigated the protective effect of TMZ alone on CIN in patients with diagnosed or suspected SCAD and preserved kidney function who underwent angiographic procedures and the variables associated with CIN development. Susceptibility to the development of CIN was demonstrated even in patients with an eGFR ≥ 60 mL/min/1.73 m². Trimetazidine only displayed an age-dependent renoprotective effect in patients undergoing coronary procedures rather than preventing CIN in all of the study group.

Patients with an eGFR ≥ 60 mL/min/1.73 m² are typically not monitored like those at risk; thus, they do not receive prophylaxis or are admitted for a longer time in the hospital to follow renal laboratory parameters. Therefore, their renal injury

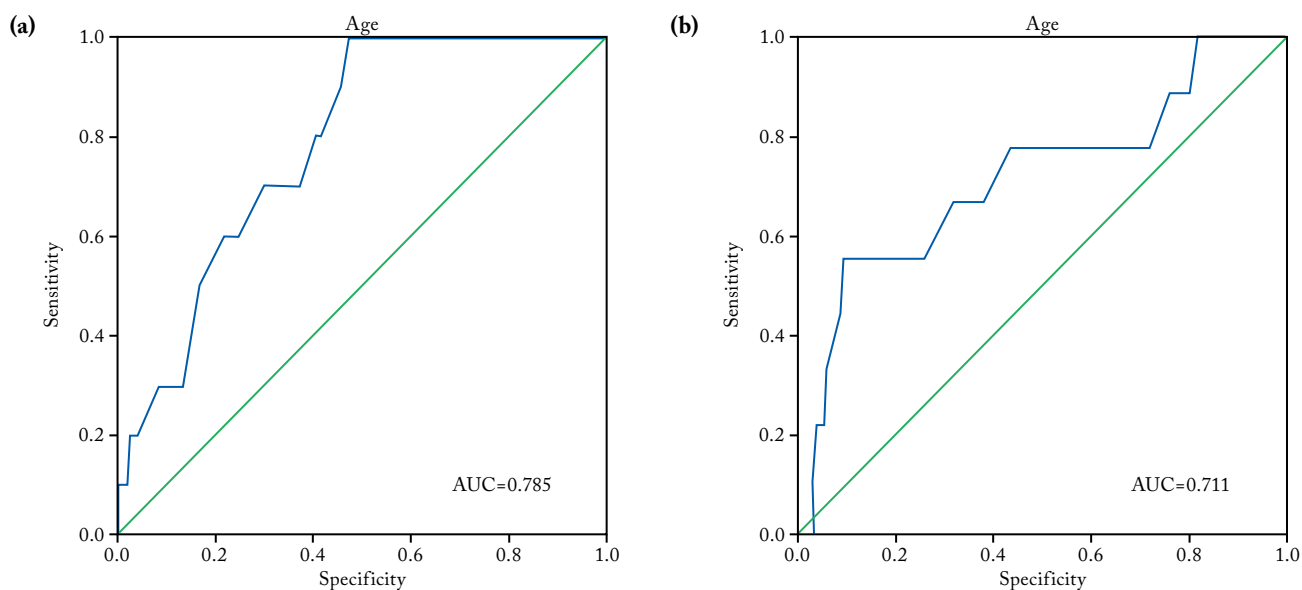


Figure 1. Receiver operating characteristic curve referring to the diagnostic performance of age in identifying patients with contrast induced nephropathy. **(a)** In patients without trimetazidine treatment and **(b)** in patients with trimetazidine treatment

might be underestimated. Our study showed that, in patients with an $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$, age was an important factor showing the vulnerability to CIN. In daily clinical practice, these patients do not receive IV hydration similar to our study, and our findings show that careful follow-up of the elderly is still warranted even, if their baseline renal function is within normal limits.

Although the complex pathophysiology of CIN still needs to be further determined. After intravascular administration of CM, a prolonged period of renal vasoconstriction develops due to imbalanced release of nitrous oxide, adenosine, endothelin, prostaglandin and reactive oxygen species (ROS) from the vascular endothelium indirect response to cytotoxicity caused by CM.^[12] The ischemic tissue prolongs the duration of vasoconstriction by secreting more harmful vasoactive ROS and other mediators.^[1]

The preservative effects of TMZ on kidney function were attributable to reducing ischemia-reperfusion injury, changes in renal glutathione reductase, catalase, and superoxide dismutase activities in animal models. However, contrary to the well-known cardiac protection of TMZ in humans, renoprotective data are still conflicting.

In a study by Onbasili et al.,^[13] CIN developed in 2.5% (1/40) of patients in the TMZ group and

in 16.6% (7/42) of patients in the non-TMZ group. TMZ, along with isotonic saline infusion, is more effective than isotonic saline alone in reducing the risk of CIN in patients with pre-existing renal dysfunction (serum creatinine level $>1.2 \text{ mg/dL}$ or $\text{eGFR} < 50 \text{ mL/min/1.73 m}^2$). In this study, serum total antioxidant capacity (TAC) decreased insignificantly after administration of CM and returned to baseline values after 2 h in both the TMZ and non-TMZ groups, with no significant difference between the treatment groups. Although no additional measurements were made at the tissue level, this finding is inconsistent with the assumption of a renoprotective effect attributed to the antioxidant effect of the drug. Shehata et al.^[14] showed an association with a reduction in the incidence of CIN and myocardial injury with TMZ intake before elective PCI in a small number of diabetic patients with mild-to-moderate renal dysfunction (eGFR of 30 to $<90 \text{ mL/min/1.73 m}^2$). In this study, patients who received IV saline, N-acetylcysteine, and TMZ were compared with those who received IV saline and N-acetylcysteine. Similarly, Ibrahim et al.,^[15] in their study including 100 patients with baseline eGFR 30 to $<90 \text{ mL/min/1.73 m}^2$ and who underwent CAG procedures, administered both groups parenteral hydration in the form of isotonic saline, while giving

TMZ treatment to one study arm. They found a significant difference in the ratio of CIN between the TMZ and non-TMZ groups (26% *vs.* 10%), but the contrast amount was significantly higher in the CIN group (165.00 ± 108.41 *vs.* 89.85 ± 38.60 , $p=0.000$).^[15] In our study, a more verifiable comparison could be made in terms of renoprotection, since there was also a treatment arm that received only TMZ without the use of IV hydration and/or N-acetylcysteine.

In the study of Chen et al.,^[16] they found that CoQ10 plus TMZ reduced the incidence of CIN in patients with renal failure ($\text{eGFR} \leq 60 \text{ mL/min/1.73 m}^2$) who underwent elective cardiac catheterization, and they attributed this result to a strong anti-oxidation effect. As this study did not separately evaluate the protective effect of CoQ10 and TMZ on CIN, it cannot emphasize the effect of TMZ alone. In the study of Mirhosseni et al.,^[17] among patients who underwent angiographic procedures with eGFR of 30 to $<60 \text{ mL/min/1.73 m}^2$, one group received saline, while another group received saline and TMZ. This study failed to show that the use of TMZ protects the development of CIN ($p>0.05$). Lian et al.^[18] showed that TMZ did not significantly decrease the risk of CIN in unselected patients undergoing PCI, even based on the alternate CIN definitions and different subgroup analyses. Since this study did not focus on specific patient groups and a high number of patients were included in the study, the results of the study may be more convenient for clinical practice. In the study of Zhang et al.,^[19] TMZ was found to be profitable in the preventive treatment of CIN occurrence in elderly diabetic patients with moderate and high risk according to MRS. In this study, patients were sub-grouped according to age ranges. Similar to our study, it was emphasized that the age factor was effective in the development of CIN.

In the Martha et al.'s^[20] systematic review and meta-analysis of seven studies involving a total of 1590 patients, the prevalence of CIN was 6% in the TMZ group and 16% in the non-TMZ group. Subgroup analysis of patients showed that TMZ reduced the risk of CIN in patients with renal impairment. However, age, BMI, hypertension, diabetes, ejection fraction, baseline serum creatinine level, and contrast medium volume were not found to be significant in the development of CIN.^[20]

The kidney is one of the fastest aging organs, and some structures and functions decline with age. It is known that oxidative stress plays a role in the pathogenesis of acute and chronic kidney disease, hypertensive and diabetic nephropathy.^[21] Nitric oxide (NO) plays a critical role in the endothelium during kidney disease and oxidative stress. Low NO levels induce the expression of anti-oxidative genes and contribute to the protection of renal endothelial and mesangial cells from apoptosis and fibrosis.^[22] We predict that TMZ reduces kidney damage with its antioxidant activity, particularly in elderly patients. Trimetazidine improves endothelium-dependent relaxation (EDR), increases NO bioavailability, and decreases ROS levels.^[23]

Nonetheless, this study has certain limitations that need to be addressed. First, although power analysis was performed, our results need to be validated in larger prospective clinical trials. Second, relatively low-risk patients ($\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$) were included in this study; thus, high-risk patients should be investigated further. Third, although patients were followed adequately for CIN occurrence according to the recommendations, following patients for a longer period would have yielded more favorable results. Finally, the mechanism of the protective effect of TMZ in a relatively older population still remains unclear and should be investigated in future studies.

In conclusion, the development of CIN should be considered even in patients with an $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$ scheduled for CAG. Risk factors should be carefully observed before and after the use of CM, particularly in elderly patients, and it should be kept in mind that the use of TMZ may be beneficial, particularly in elderly patients with appropriate indications.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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