Original article

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Contrast-induced kidney injury: how does it affect long-term cardiac mortality?

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Aims **Contrast-induced acute kidney injury (CIAKI) is a common complication after coronary angiography or percutaneous revascularization (PCI). This study aimed to investigate the association of CIAKI with long-term cardiovascular adverse events.**

Methods **In total, 980 patients undergoing coronary angiography/PCI were assessed in this prospective cohort study. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE) and cardiac death (CVD) during an 8-year follow-up. Glomerular filtration rate change during the follow-up was the secondary endpoint.**

CIAKI was defined as a serum creatinine increase at least 0.3 mg/dl in 48 h or at least 50% in 7 days.

Results **CIAKI was observed in 69 patients (7%). Chronic kidney disease [relative risk (RR) = 4, $P<0.01$], reduced ejection fraction (RR = 2.88, $P<0.01$), CIAKI risk score at least 4 (RR = 2.64, $P=0.02$), and emergency coronary angiography/PCI (RR = 3.87, $P<0.01$) increased CIAKI risk, whereas statins were protective (RR = 0.32, $P<0.01$).**

Patients with CIAKI had higher rates of 8-year cardiovascular adverse events: 54 versus 15% MACCE (RR = 6.67, $P<0.01$), 38 versus 4% CVD (RR = 15.73, $P<0.01$). Among other factors, CIAKI was the strongest predictor of 8-year MACCE (RR = 3.16, $P<0.01$) and CVD (RR = 7.34, $P<0.01$).

During the follow-up, glomerular filtration rate declined drastically in CIAKI patients: 70 versus 39% had chronic kidney disease stage worsening ($P<0.01$) and 8 versus 0.3% started hemodialysis ($P<0.01$).

Conclusion **We found a strong correlation between CIAKI and poor long-term cardiac outcomes. Apparently showing up as a transient, functional impairment of kidney function, CIAKI implies an organic damage with structural modifications leading to significant kidney deterioration over time, responsible for an increased risk of long-term cardiac events. Statins significantly reduced CIAKI occurrence. A careful management of high-risk patients is needed to limit long-term complications of coronary angiography/PCI.**

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Keywords: contrast-induced acute kidney injury, coronary angiography, major adverse cardiac and cerebrovascular events, statins, uremic memory

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Introduction

Contrast-induced acute kidney injury (CIAKI) is a common complication in patients undergoing coronary angiography or percutaneous revascularization (PCI). Depending on risk factors such as compromised glomerular filtration rate (GFR), advanced age, reduced left ventricular ejection fraction (LVEF), diabetes and contrast media volume, CIAKI may occur in more than one-third of patients undergoing coronary angiography/PCI.[1–3] Despite the existence of more than 35 definitions in the literature[4,5] CIAKI is currently defined[6,7] as an increase in serum creatinine (sCr) at least 0.3 mg/dl in 48 h, or at least 50% in 7 days after any procedure requiring contrast media. As PCI is constantly increasing in the elderly, affected by a physiological decline in renal function (approximately 8 ml/min/1.73 m^2 GFR reduction/decade after 30 years of age[8]), CIAKI prevention has become an emerging cardiologic issue. Common preventive treatments are antioxidative agents, hydration, and high-volume forced diuresis with matched hydration.[6,9] In patients with CIAKI, an increased rate of both cardiovascular events [acute coronary syndrome (ACS), heart failure] and cerebrovascular events (transient ischemic attack, ischemic stroke, haemorrhagic stroke) has been reported in the literature.[1–3] A 13-fold increased risk of death at 1 month and a 6-fold increased risk of death at 1 year was observed in patients with CIAKI following PCI.[10] However, whether and how

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CIAKI independently affects cardiac mortality in the long term remains a challenging issue.[11] The aim of this study was to investigate the association of CIAKI with long-term cardiac adverse events and to identify possible risk and protective factors for CIAKI.

Methods

This prospective cohort study assessed 980 consecutive patients undergoing coronary angiography/PCI in our center between November 2006 and December 2007. End-stage renal disease on hemodialysis, cardiogenic shock, mechanical ventilation, simultaneous cancer disease, or multiple myeloma were exclusion criteria.

The primary endpoint was 8-year MACCE [cumulative endpoint defined as: ACS, acute pulmonary edema, cardiogenic shock, transient ischemic attack, stroke, cerebrovascular death, cardiac death (CVD)] and 8-year CVD. The secondary endpoint was GFR change during the follow-up. After having ruled out other possible causes of acute kidney injury, CIAKI was diagnosed if a sCr increase at least 0.3 mg/dl in 48 h, or at least 50% in 7 days was observed following coronary angiography/PCI. CIAKI was staged according to guidelines criteria,[6] that is: stage III, sCr increase more than three-fold from baseline or at least 4 mg/dl, or dialysis; stage II, sCr increase more than two-fold from baseline; stage I, other forms of CIAKI with a milder sCr increase. Chronic kidney disease (CKD) stage was established according to guidelines criteria[12]: stage G4 for GFR between 15 and 29 ml/min/1.73 m^2, stage G3b for GFR between 30 and 44 ml/min/1.73 m^2, stage G3a for GFR between 45 and 59 ml/min/1.73 m^2, stage G2 for GFR between 60 and 89 ml/min/1.73 m^2, stage G1 for GFR at least 90 ml/min/1.73 m^2.

Coronary angiography/PCI was performed through femoral or radial artery. Iso-osmolar dimeric contrast media iodixanol (320 mg/ml iodine concentration and 290 mOsm/kg water; Visipaque Amersham Health, Oslo, Norway) was used in all procedures. According to our department protocol for CIAKI prevention, routine prophylactic in vein hydration was performed to all patients with isotonic saline, given intravenously at a rate of 1 ml/kg body weight/h (0.5 ml/kg for patients with LVEF <40%) for 12 h before and 18 to 24 h after PCI, unless for emergent patients. Patients with a preprocedural GFR less than 60 ml/min/1.73 m^2 received in vein hydration with 154 mEq/l sodium bicarbonate in 5% dextrose and water. The initial intravenous bolus was 3 ml/kg/h (maximum 200 ml/h) for 1 h before contrast media injection. After this, patients received the same fluid at a rate of 1 ml/kg/h (maximum 110 ml/h) for 6 h after the procedure. All patients received N-acetylcysteine orally at a dose of 1200 mg and vitamin C at a dose of 5000 mg, both given twice daily on the day before and the day of administration of the contrast media (total 2 days). All diabetic patients on hypoglycemic treatment were temporarily replaced with insulin therapy before the procedure, whereas angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers were temporarily suspended or replaced with other antihypertensive drugs, if needed. Laboratory tests were assessed at baseline and 48–72 h after angiography. All patients not requiring more than 3 days of hospitalization were discharged with indication to repeat sCr evaluation within 7 days in our laboratory. Furthermore, sCr was assessed at 5 years after discharge. The conventional alkaline picrate method (Jaffe) was used for sCr measurement. sCr was used to estimate GFR with CKD epidemiology collaboration equation.[13] An oral and written informed consent was given from all patients before coronary angiography/PCI. Clinical data about the index hospitalization were collected with direct patient interrogation. We assessed in all patients cardiovascular risk factors, renal function, recent and past medical history. Patients were stratified according to the Mehran[1] risk score for CIAKI. All available patients were assessed during an 8-year follow-up by direct patient interrogation or medical outpatient visits as to enquire their health status following discharge, with particular care to the occurrence of any MACCE or renal function worsening. Information on unavailable patients was obtained from electronic medical records or from the referring primary care physician.

Continuous variables, presented as means and SD, were compared by nonparametric tests: Mann–Whitney's test was used for independent data and Wilcoxon's signed-rank test for paired data (pre-post evaluations). Categorical variables, presented as counts and percentages, were compared using the χ^2 test with Yates' correction or Fisher's exact test. All analyses were performed using the SPSS for Windows version 18.0 (SPSS, Inc., Chicago, Illinois, USA) and a two-sided significance level of less than 0.05 was considered statistically significant. The survival probability and the freedom from adverse events were evaluated with the Kaplan–Meier curves, compared by the Mantel–Cox test. Univariate logistic analysis was used to determine the association between risk factors and CIAKI. Multivariate logistic regression and Cox regression analysis were performed to examine the effects of different possible confounding variables on the incidence of CIAKI or adverse events during follow-up. The relative risk (RR) was computed with its 95% confidence interval (CI).

Results

Overall, 980 patients were enrolled in this prospective cohort study. Mean age was 66 ± 11 years (range 31–88) and mean GFR was 78 ± 20 ml/min/1.73 m^2 (range 19–130). Detailed baseline and clinical data are described in Table 1.

Following coronary angiography/PCI, CIAKI was observed in 69 patients (7%). Among them, 57 patients

Table 1 Characteristics of study participants

	Population ($n=980$)	CIAKI ($n=69$)	No CIAKI ($n=911$)	*P* value
Age (years)	66 ± 11	72 ± 8	66 ± 11	<0.01
BMI (kg/m^2)	27 ± 4	27 ± 5	27 ± 4	0.44
Female sex	274 (28%)	20 (29%)	254 (28%)	0.89
LVEF on admission <40%	116 (12%)	25 (36%)	91 (10%)	<0.01
Smokers	261 (27%)	12 (17%)	249 (27%)	0.09
Hypertension	739 (75%)	55 (80%)	684 (75%)	0.47
Diabetes	197 (20%)	22 (32%)	175 (19%)	0.02
Dyslipidemia on chronic statin treatment	548 (56%)	26 (38%)	522 (57%)	<0.01
CAD	463 (47%)	33 (48%)	430 (47%)	0.99
Prior AMI	260 (27%)	19 (27%)	241 (27%)	0.88
Baseline sCr (mg/dl)	0.97 ± 0.3	1.2 ± 0.5	0.95 ± 0.3	<0.01
Baseline GFR (ml/min/1.73 m^2)	78 ± 20	61 ± 23	79 ± 19	<0.01
GFR <60 ml/min/1.73 m^2	184 (19%)	38 (55%)	146 (16%)	<0.01
β-blockers[a]	703 (72%)	46 (67%)	657 (72%)	0.33
CCBs[a]	232 (24%)	20 (29%)	212 (23%)	0.30
ACE-inhibitors[a]	706 (72%)	52 (75%)	654 (72%)	0.58
ARBs[a]	85 (9%)	3 (4%)	82 (9%)	0.26
In-hospital statin administration	696 (71%)	34 (49%)	662 (67%)	<0.01
CIAKI risk score[b]	4.1 ± 3.2	7.2 ± 3.8	3.8 ± 3	<0.01
CM volume (ml)	234 ± 155	288 ± 194	230 ± 150	<0.01
PCI	572 (58%)	45 (65%)	527 (58%)	0.26
Emergency CA/PCI	192 (20%)	30 (43%)	162 (18%)	<0.01
Diagnosis on admission				
STEMI	164 (17%)	25 (36%)	139 (15%)	<0.01
NSTEMI	123 (13%)	16 (23%)	107 (12%)	0.01
UA	374 (38%)	15 (22%)	359 (39%)	<0.01
Stable angina	125 (13%)	2 (3%)	123 (13%)	<0.01
Signs of myocardial ischemia on non-invasive tests	163 (17%)	2 (3%)	161 (18%)	<0.01
Decompensated heart failure	31 (3%)	9 (13%)	22 (2%)	<0.01

ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ARBs, angiotensin-II receptor blockers; CA, coronary angiography; CAD, coronary artery disease; CCBs, calcium-channel-blockers; CIAKI, contrast-induced acute kidney injury; CM, contrast media; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous revascularization; sCr, serum creatinine; STEMI, ST segment elevation myocardial infarction; UA, unstable angina. [a]On chronic treatment at hospital admission. [b]According to Mehran equation.

were classified as CIAKI stage I, five patients as stage II, and seven patients as stage III.

Advanced age (>75-years old), compromised LVEF (<40%), CKD (GFR <60 ml/min/1.73 m^2), diabetes mellitus, elevated CIAKI risk score (≥4), high amount of contrast media during coronary angiography/PCI (>300 ml), female sex, emergency coronary angiography/PCI and statins treatment correlated with CIAKI diagnosis and were further evaluated in a multivariate analysis to confirm their prognostic role. At the multivariate analysis CKD, emergency coronary angiography/PCI, compromised LVEF, elevated CIAKI risk score, and statins treatment were the strongest factors, independently correlated with CIAKI, as shown in Table 2.

CKD was the most important risk factor for CIAKI (RR = 4). Indeed, CKD patients had a higher incidence of CIAKI compared with patients with normal renal function (21 versus 4%, $P < 0.01$). CIAKI incidence increased across worse CKD stages, varying between 4 and 50%, as shown in Table 3.

An important CIAKI risk factor was emergency coronary angiography/PCI (RR = 3.87). In total, 192 patients (20%) underwent an emergency procedure, suffering a higher CIAKI incidence compared with patients with a deferred/scheduled procedure: 15 versus 5%, *P* value less than 0.01. Patients treated with an emergency procedure received larger amounts of contrast media (276 ± 177 versus 225 ± 147 ml, $P < 0.01$) during longer procedures (68 ± 33 versus 57 ± 34 min, $P < 0.01$) most times without a complete preprocedural CIAKI prophylaxis because of timing reasons.

After a stratification for admission diagnosis we observed that CIAKI occurred in 9/31 (29%) patients with decompensated heart failure, 25/164 (15%) patients with ST segment elevation myocardial infarction, 16/123 (13%) patients with non-ST segment elevation myocardial

Table 2 Contrast-induced acute kidney injury risk/protective factors: multivariate regression analysis of the baseline factors correlated with contrast-induced acute kidney injury diagnosis

	CIAKI		
	RR	95% CI	*P* value
GFR <60 ml/min/1.73 m^2	4	[2.2–7.3]	<0.01
Emergency CA/PCI	3.87	[2.2–6.9]	<0.01
LVEF on admission <40%	2.88	[1.6–5.3]	<0.01
CIAKI risk score ≥4	2.64	[1.1–6.1]	0.02
Contrast media volume >300 ml	1.73	[0.9–3.1]	0.07
Diabetes mellitus	1.16	[0.6–2.2]	0.66
Age >75 years	0.99	[0.8–1.2]	0.89
Female sex	0.89	[0.5–1.6]	0.69
Statins treatment	0.32	[0.2–0.6]	<0.01

CA, coronary angiography; CIAKI, contrast-induced acute kidney injury; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; PCI, percutaneous revascularization; RR, relative risk.

Table 3 Contrast-induced acute kidney injury incidence according to chronic kidney disease severity

	Patients	CIAKI incidence
G1 (GFR ≥90 ml/min/1.73 m^2)	322 (33%)	3.7%
G2 (GFR 60–89 ml/min/1.73 m^2)	474 (48%)	4%
G3a (GFR 45–59 ml/min/1.73 m^2)	119 (12%)	11.8%
G3b (GFR 30–44 ml/min/1.73 m^2)	57 (6%)	35%
G4 (GFR 15–29 ml/min/1.73 m^2)	8 (1%)	50%

CIAKI, contrast-induced acute kidney injury; GFR, glomerular filtration rate.

infarction, 15/374 (4%) patients with unstable angina, 2/163 (1%) patients with signs of myocardial ischemia on non-invasive tests and 2/125 (2%) patients with stable angina.

Statins treatment prior to coronary angiography/PCI was found to be a protective factor (RR = 0.32) for CIAKI. In-hospital statin administration was continued in 548 (56%) patients already on chronic treatment, whereas it was started on admission in further 148 (15%) patients. CIAKI was observed in 26/548 (5%) patients on chronic treatment and in 8/148 (5%) patients receiving statins on admission, whereas it occurred in 35/284 (12%) patients not assuming statins, $P < 0.01$ between patients assuming statins and not assuming statins.

The CIAKI risk score estimated with Mehran equation had a worthy predictive value in the present study as those with a score equal or greater than four had a more than doubled risk for CIAKI (RR = 2.64).

Major adverse events and mortality in patients with contrast-induced acute kidney injury

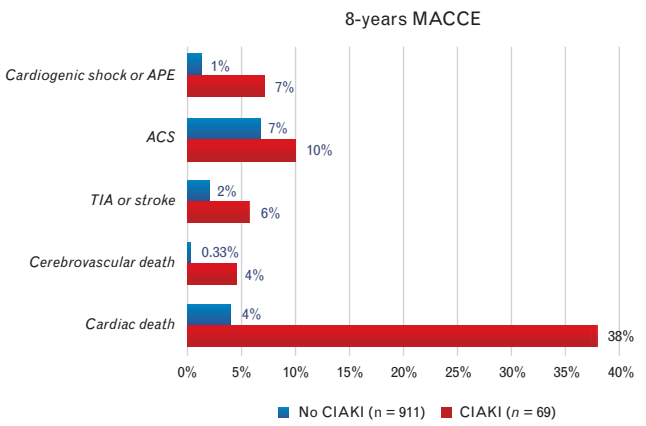
After coronary angiography/PCI, 16 (2%) patients died soon before discharge of cardiovascular complications. Among them, 62% had previously developed a postprocedural CIAKI, P value less than 0.01. In-hospital mortality was 10/69 (14%) in patients who developed CIAKI after the index procedure versus 6/911 (0.7%) other patients (RR = 25.3, 95% CI 8.9–77.5).

Over the entire 8-year follow-up period, an overall number of 141 MACCE were observed. Patients with CIAKI had a higher incidence of MACCE at 8 years (54 versus 15%, RR = 6.67, 95% CI 3.8–11.7). MACCE distribution is shown in Fig. 1.

During the 8-year follow-up, 127 patients died. Postprocedural CIAKI was associated with increased 8-year cardiac mortality rates (38 versus 4%, RR = 15.73, 95% CI 8.1–30.6) and cerebrovascular mortality rates (4 versus 0.3%, RR = 13.66, 95% CI 2.3–80.9). The incidence of adverse events during the follow-up is described in Fig. 2, whereas Kaplan–Meier survival curves are reported in Fig. 3.

As to further investigate the association of CIAKI with adverse outcomes, a univariate analysis was carried out

Fig. 1



Eight-year major adverse cardiac and cerebrovascular events distribution. ACS, acute coronary syndrome; APE, acute pulmonary edema; CIAKI, contrast-induced acute kidney injury; MACCE, major adverse cardiac and cerebrovascular events; TIA, transient ischemic attack.

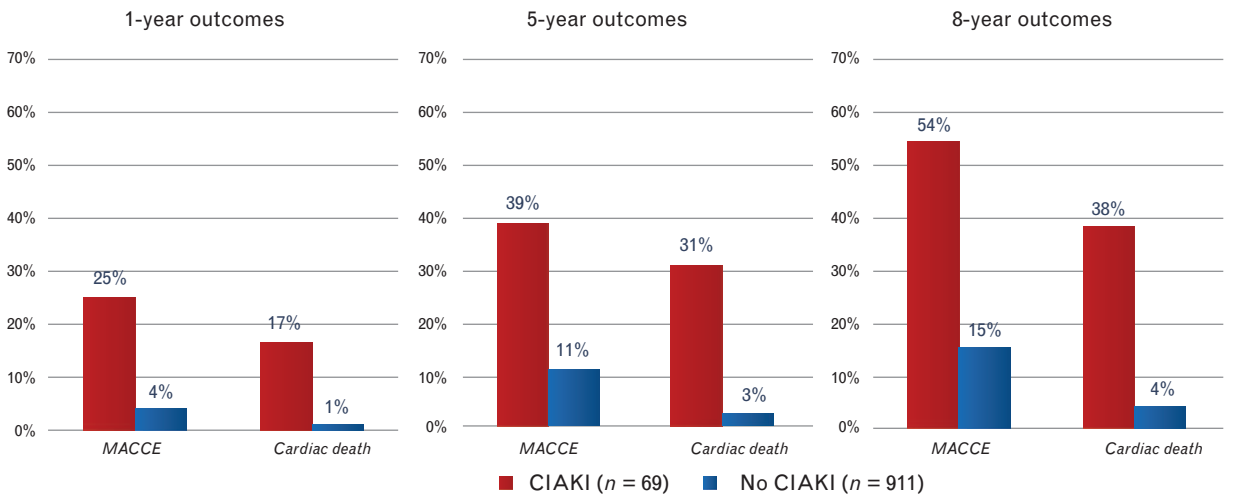
and the following variables showed a significant correlation with the risk of developing MACCE and/or cardiac death at 8 years: advanced age, reduced LVEF, hypertension, CKD, diabetes mellitus, emergency coronary angiography/PCI, elevated CIAKI risk score, CIAKI, and statins treatment. Such factors were further evaluated with a Cox regression analysis to appraise the independent weight of each factor on adverse event occurrence over time (Table 4). CIAKI was found to be the most important risk factor for 8-year cardiac death (RR = 7.34) and 8-year MACCE (RR = 3.16). On the contrary, statins had a powerful independent protective role over 8-year cardiac death (RR = 0.34) and 8-year MACCE (RR = 0.70).

Renal function assessment during the follow-up

As to appraise the long-term renal outcome among patients with CIAKI, GFR change was assessed at 5 years after discharge. Despite a decrease of GFR over time in the whole population ($P < 0.01$), those patients developing CIAKI suffered a greater and faster deterioration of renal function over time (Fig. 4): indeed, during follow-up GFR was 44 ± 26 versus 69 ± 44 ml/min/1.73 m^2 ($P < 0.01$). Furthermore, the mean GFR annual decrease rate was -4.4 ± 5.2 versus -2.5 ± 5.3 ml/min/1.73 m^2/year ($P < 0.01$).

Most patients with CIAKI had a CKD stage worsening (of one or more stages) during the follow-up, opposite to patients who did not show CIAKI (70 versus 39%, RR = 3.61, 95% CI 1.8–7.2), as described in Fig. 5. Furthermore, patients with CIAKI needed more frequently to start on hemodialysis during the follow-up (8 versus 0.3%, RR = 28, 95% CI 6.9–142).

Fig. 2



Long-term outcomes of patients with contrast-induced kidney injury. CIAKI, contrast-induced acute kidney injury; MACCE, major adverse cardiac and cerebrovascular events.

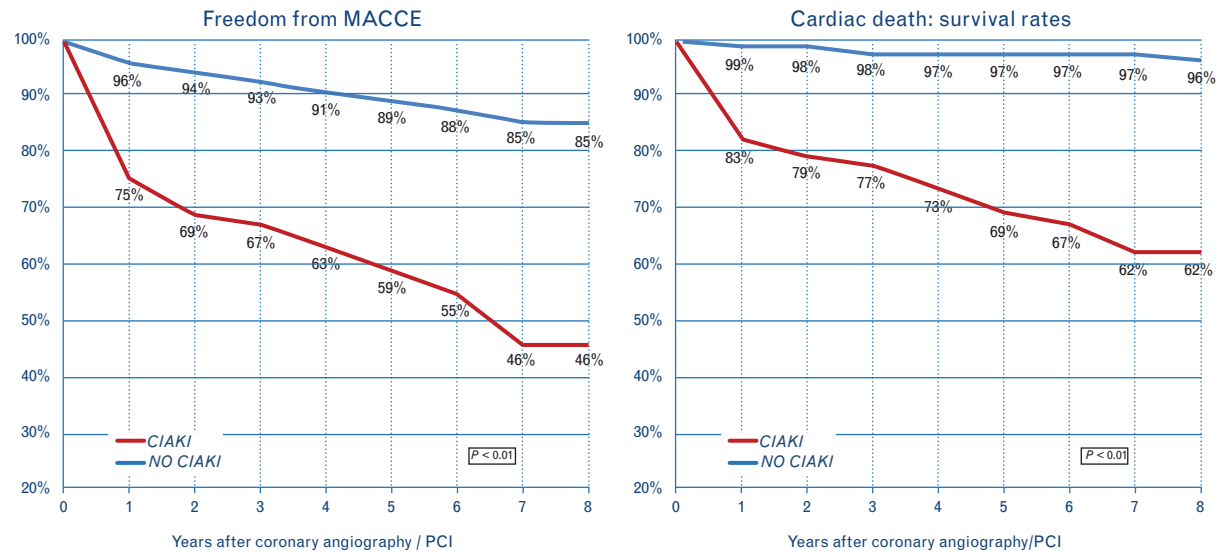
As to further investigate the association of CKD stage worsening with long-term cardiac outcomes, we observed that such patients had a worse prognosis compared with those without CKD worsening: 29 versus 15% MACCE ($P < 0.01$), 9 versus 1% cardiac death ($P < 0.01$).

In total, seven patients diagnosed with CIAKI stage III, compared with patients with CIAKI stage I-II, underwent an even worse deterioration of renal function: CKD stage worsening was observed in all seven patients (100 versus 68% other CIAKI patients, $P = 0.66$); hemodialysis was required in one patient (14 versus 8% other CIAKI patients, $P = 0.97$).

Discussion

Contrast-induced nephropathy is a well known complication of angiographic procedures associated with lengthened hospital stay and poorer early and long-term outcomes.[1–3] The Mayo Clinic PCI registry study[3] showed that patients after CIAKI continued to be at

Fig. 3



Kaplan–Meier survival curves in patients with CIAKI. CIAKI, contrast-induced acute kidney injury; MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous revascularization.

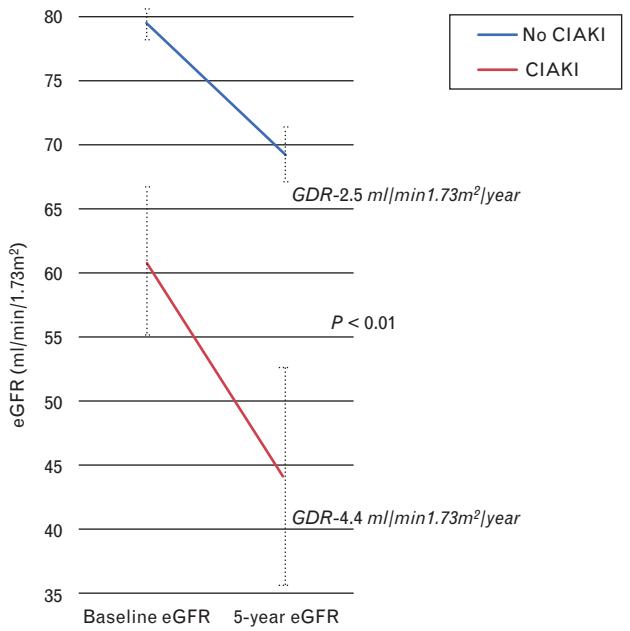
Table 4 **Cox regression analysis: 8-year risk of adverse events**

	8-year cardiac death			8-year MACCE		
	RR	95% CI	*P* value	RR	95% CI	*P* value
CIAKI	7.34	[3.6–14.8]	<0.01	3.16	[2.0–4.9]	<0.01
LVEF on admission <40%	4.41	[2.3–8.4]	<0.01	1.96	[1.3–2.9]	<0.01
Age >75 years	2.66	[1.2–5.7]	0.01	2.01	[1.3–3.2]	<0.01
Diabetes mellitus	2.25	[1.1–4.5]	<0.01	2.16	[1.4–3.2]	<0.01
Emergency CA/PCI	1.25	[0.6–2.5]	0.51	1.49	[1.1–2.2]	0.04
Hypertension	1.21	[0.6–2.6]	0.61	1.34	[0.9–2]	0.20
CIAKI risk score ≥4	0.98	[0.4–2.3]	0.96	0.87	[0.5–1.4]	0.58
GFR <60 ml/min/1.73 m^2	0.63	[0.3–1.3]	0.24	1.04	[0.7–1.6]	0.85
Statins treatment	0.34	[0.2–0.6]	<0.01	0.70	[0.5–0.9]	0.04

CA, coronary angiography; CI, confidence interval; CIAKI, contrast-induced acute kidney injury; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous revascularization, RR, relative risk.

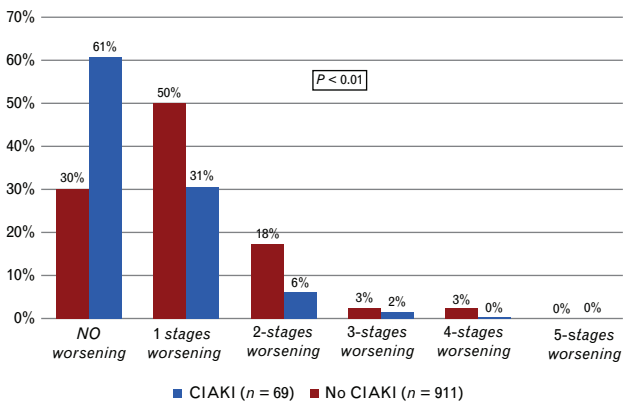
higher risk of adverse events during a long-term follow-up: overall survival was lower for patients who experienced CIAKI, compared with other patients (88 versus 96% at 1 year and 55 versus 85% at 5 years, respectively, $P<0.01$). Differently from previous reports, a recent Korean study[14] on 297 CKD patients undergoing PCI demonstrated that CIAKI was significantly associated not only with 2-year all-cause mortality (42 versus 16%, $P<0.01$) but also with cardiac mortality (24 versus 10%, $P<0.01$). In our study CIAKI was significantly associated with increased rates of long-term adverse events such as cardiac mortality (16-fold increased risk at 8 years, 38 versus 4%), cerebrovascular mortality (14-fold increased risk at 8 years, 4 versus 0.3%) and MACCE (7-fold increased risk at 8 years, 54 versus 15%).

Fig. 4



Renal function variation during follow-up. GDR, mean glomerular filtration rate annual decrease rate. CIAKI, contrast-induced acute kidney injury; GDR, glomerular filtration rate annual decrease rate; eGFR, estimated glomerular filtration rate.

Fig. 5



CKD stage worsening during follow-up. CIAKI, contrast-induced acute kidney injury; CKD, chronic kidney disease.

Although these findings suggest a correlation between CIAKI and long-term cardiac mortality, some clinical considerations are needed to explain these apparently unforeseen results. Indeed, as CIAKI occurrence is influenced by several risk factors and comorbidities (i.e. compromised GFR, advanced age, reduced LVEF, diabetes, and contrast media volume[1–3]), it is questionable whether CIAKI has a direct effect on mortality or is simply a marker of frailty, occurring frequently in more frail patients with an intrinsic higher risk of death. Furthermore, in the vast majority of CIAKI cases, sCr values apparently normalize in 5–10 days. Whether and how CIAKI could directly affect long-term cardiac mortality has been an unsolved open matter of debate, and was the main aim of the present study.

In an effort to investigate the possible cause-effect relationship between CIAKI and long-term cardiovascular adverse events, we found that it was the most important risk factor for 8-year cardiac death (RR = 7.34) and MACCE (RR = 3.16), independently of other concurrent but less influential factors such as advanced age, reduced LVEF, hypertension, CKD, diabetes, emergency coronary angiography/PCI, and elevated CIAKI risk score. This finding of our study means that CIAKI is directly and independently associated with cardiac outcomes: but how?

CIAKI pathogenesis involves renal tubular damage and medullary hypoxia because of contrast media-induced vasa recta constriction, drastically amplified by endothelial dysfunction, inflammation, and oxidative stress.[15] The consequent release of substances such as angiotensin,

endothelin, tumor necrosis factor alpha, and inflammatory cytokines may produce itself a myocardial damage.[16,17] In addition, in animal models acute kidney injury was associated not only with functional alterations (i.e. transient decrease of GFR) but also with structural changes such as glomerulotubular disconnection, that is supposed to be responsible for the long-term detrimental effects on renal function.[18] Although functional alterations apparently recover quickly, interstitial fibrosis, atubular glomeruli and a high interstitial-to-glomerular ratio represent the histologic imprints of a past event of kidney injury, consistent with an increased risk of CKD progression over time. The model of 'uremic memory' was hypothesized by Golestaneh *et al.*[19] to explain the long-term effects of acute kidney injury. According to Zager,[20] acute kidney injury triggers a cellular reprogramming with persistent upregulation of proinflammatory, profibrotic, and vasoconstrictive genes, culminating in progressive renal injury and extrarenal tissue injury (i.e. organ 'cross-talk'). A Canadian study[21] on patients undergoing coronary angiography revealed a linear correlation between acute kidney injury severity and loss of kidney function at 3 and 12 months following the procedure.

The findings of the present study are consistent with the aforementioned mechanisms: indeed, it was observed that CIAKI was able to accelerate kidney function deterioration beyond the ranges of physiological aging,[8] with a statistically relevant change in mean GFR in the long-term (GFR annual decrease rate -4.4 ± 5.2 versus -2.5 ± 5.3 ml/min/1.73 m^2/year, $P < 0.01$). Patients with CIAKI had a nearly quadrupled increased risk of CKD stage worsening ($P < 0.01$).

Furthermore, it has been reported in the literature that an accelerated progression of renal dysfunction[22–24] is a well known risk factor able to enhance vascular, endothelial, and atherosclerotic damage evolution[25–27] leading to cardiovascular complications untill cardiac death. Indeed, appraising the prognostic significance of CKD stage worsening in our population, it was found to be associated with an increased rate of long-term cardiac events: 29 versus 15% for 8-year MACCE (<0.01), 9 versus 1% for 8-year cardiac death ($P < 0.01$).

In addition to the aforementioned findings, it is important to notice that statins administration was found to be a protective factor for CIAKI (RR = 0.32, $P < 0.01$). In patients undergoing PCI, a high systemic inflammatory status is usually associated with an increased risk of periprocedural complications and cardiac events.[28] Widely used in the setting of coronary artery disease because of their cholesterol-lowering effect, statins can also improve endothelial function, enhance atherosclerotic plaques stability, decrease oxidative stress and inflammation (i.e. statins pleiotropic effects).[29] Considering CIAKI pathophysiology, statins pleiotropic effects appear to be beneficial to counterbalance contrast media toxicity. The atorvastatin for reduction of myocardial damage during angioplasty–contrast-induced nephropathy trial demonstrated that short-term pretreatment with high-dose atorvastatin in ACS patients can significantly decrease the occurrence of CIAKI.[30] In the study by Patti *et al.*,[31] patients receiving statins before PCI had a significant decrease of CIAKI; this early protective effect translates into better long-term event-free survival. The protective effect of rosuvastatin and antiplatelet therapy on CIAKI and myocardial damage in patients with ACS study[32] shows that high-dose rosuvastatin given on admission in ACS patients reduced CIAKI and 30-day adverse cardiovascular and renal events. Our results are in agreement with the literature, supporting the prophylactic administration of statins prior to coronary angiography/PCI to prevent CIAKI. The latest European society of cardiology guidelines on myocardial revascularization recommends statins use to prevent CIAKI, especially in high-risk patients.

Study limitations

The study has some limitations, that is, it is monocentric, and therefore our observations are limited to our hospital catchment area. Coronary angiography/PCI procedures in the emergency setting necessitated larger amounts of contrast media and this might have influenced the CIAKI rates as aforementioned. As to renal function evaluation during the follow-up, sCr was used as the only surrogate marker of renal function. Furthermore, the possible discontinuation of any prescribed drugs during the follow-up was not investigated.

Conclusion

In our cohort of patients undergoing coronary angiography/PCI, a strong correlation was found between CIAKI and poor long-term cardiac outcomes. Investigating a possible cause-effect relationship upon this correlation, we found that our data were in agreement with the theoretical model of uremic memory along with different studies in the literature: apparently showing up as a transient functional compromission of kidney function, CIAKI implies an organic damage along with structural modifications leading to faster kidney deterioration over time. The accelerated decline of kidney function observed in CIAKI patients is responsible for an increased risk of cardiovascular complications in the long term.

Preprocedural administration of statins had significantly reduced the risk of CIAKI. A careful assessment of patients at risk for CIAKI along with proper preventive measures are of primary importance to limit the iatrogenic damage of coronary angiography/PCI.

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Conflicts of interest

There are no conflicts of interest.

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