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

CONTRAST-INDUCED KIDNEY INJURY:

HOW DOES IT AFFECT LONG-TERM CARDIAC MORTALITY?

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ABSTRACT

Aims

Contrast-Induced Acute Kidney Injury (CIAKI) is a common complication after coronary angiography (CA) or percutaneous revascularization (PCI). This study aimed to investigate the association of CIAKI with long-term cardiovascular adverse events.

Methods

One-thousand patients undergoing CA/PCI were assessed in this prospective cohort study. CIAKI was the primary end-point, defined as a creatinine increase ≥0.3 mg/dl in 48h or ≥50% in 7 days. 8-year cardiac mortality (CVD) and major-adverse-cardiac-and-cerebrovascular-events (MACCE) were secondary end-points. Glomerular filtration rate (GFR) during the follow-up was the tertiary end-point.

Results

CIAKI was observed in 74 patients (7.4%). Chronic kidney disease (CKD) (RR=3.61,p<0.01), reduced ejection fraction (RR=2.70,p<0.01) and CIAKI risk score ≥6 (RR=2.23,p=0.03) at admission, plus emergency CA/PCI (RR=3.54,p<0.01) increased CIAKI risk, while statin treatment (chronic or given-on-admission) was protective (RR=0.41,p<0.01). Patients with CIAKI had higher adverse events rates: 15% vs.1% in-hospital mortality (RR=26.77,p<0.01), 19% vs. 1% 1-year CVD (RR=17.77,p<0.01), 26% vs. 4% 1-year MACCE (RR=7.65,p<0.01), 40% vs.4% 8-year CVD (RR=16.82,p<0.01), 56% vs. 15% 8-year MACCE (RR=6.99,p<0.01). CIAKI was the strongest predictor of 8-year CVD (RR=7.72,p<0.01) and MACCE (RR=3.27, p<0.01). During the follow-up, GFR declined significantly in CIAKI patients: 32% vs.19% had CKD stage worsening (p<0.01) and 11% vs.0.3% started haemodialysis (p<0.01).

Conclusion

We found a strong correlation between CIAKI and poor short- and long-term cardiac outcomes, possibly due to

an accelerated progression of renal dysfunction. Pre-procedural administration of statins had significantly reduced the risk of CIAKI. A careful assessment and management of high-risk patients is needed to limit the possible acute and long-term complications of CA/PCI.

Keywords: Contrast-Induced Acute Kidney Injury; Major-adverse-cardiac-and-cerebrovascular-events; Statins; Percutaneous revascularization.

INTRODUCTION

Contrast-Induced Acute Kidney Injury (CIAKI) is a common complication in patients undergoing coronary angiography (CA) 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 CM volume, CIAKI may occur in more than one-third patients undergoing CA/PCI[1–3]. Despite existence of more than 35 definitions in literature[4,5] CIAKI is currently defined[6,7] as an increase in serum creatinine (sCr) ≥0.3 mg/dl in 48 hours, or ≥50% in 7 days after any procedure requiring contrast media (CM). As PCI is constantly increasing in the elderly, affected by a physiological decline in renal function (approximately 8 ml/min/1.73m^2 GFR reduction/decade after 30 years of age[8]), CIAKI prevention has become an emerging cardiologic issue. Common preventive treatment are anti-oxidative 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 (TIA), ischemic stroke, haemorrhagic stroke) has been reported in literature(2, 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 CIAKI independently affects cardiac mortality in the long-term remains a challenging issue[11]. The aims of this study were: to investigate the possible association of CIAKI with long-term mortality and cardiac events; to identify risk and protective factors for CIAKI. Primary end-point was CIAKI following CA/PCI, defined as sCr increase ≥0.3 mg/dl in 48 hours or +50% in 7 days. Secondary end-points were 8-year cardiac mortality and MACCE (defined as: ACS, acute pulmonary edema (APE), cardiogenic shock, TIA, stroke, cardiovascular or cerebrovascular death). Tertiary end-point was GFR during the follow-up.

METHODS

Study design

This prospective cohort study assessed 1000 consecutive patients undergoing CA/PCI in our centre between November 2006 and December 2007. Cardiogenic shock, mechanical ventilation, simultaneous cancer disease or multiple myeloma were exclusion criteria.

Study protocol

CA/PCI was performed through femoral or radial artery. Iso-osmolar dimeric CM iodixanol (320 mg/ml iodine concentration and 290 mOsm/kg water; Visipaque Amersham Health, Oslo, Norway) was used in all procedures.

Patients with chronic kidney disease (CKD), assumed as a baseline eGFR<60 ml/min/1.73m^2 (computed according to the Chronic Kidney Disease EPIdemiology collaboration equation[12]) were given specific CIAKI prophylaxis according to our department protocol: in vein (i.v.) hydration with 0.9% NaCl isotonic saline solution, infusion rate 1 ml/kg body weight per hour for 12 hours (reduced to 0.5 ml/kg/h if LVEF<40%) before CA/PCI and for 18-24 hours after CA/PCI; i.v. 1.4% sodium bicarbonate solution (SB), infusion rate 3 ml/kg/h (maximum 200 ml/h) for 1 hour before procedure and 1 ml/kg/h for 6 hours after CA/PCI (maximum 110 ml/h); oral N-acetylcysteine 1200 mg twice daily the day before and on procedure day; oral Vitamin C 5000 mg on procedure day and 5000 mg the following day. CKD patients undergoing emergency procedures could not receive a complete pre-procedural CIAKI prophylaxis because of timing reasons. All patients with End-Stage Renal Disease (ESRD) on hemodialysis received an additional dialytic session after CA/PCI, according to our department protocol. Diabetics on hypoglycemic treatment were temporarily replaced with insulin therapy before procedure, while Angiotensin Converting Enzyme (ACE) inhibitors or Angiotensin-II Receptor Blockers (ARBs) were temporarily suspended or replaced with other antihypertensive drugs, if needed.

Laboratory tests were assessed at baseline and 48 to 72 hours 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 year after discharge in each patient. The conventional alkaline picrate method (Jaffe) was used for sCr measurement.

After having ruled out other possible causes of acute kidney injury, CIAKI was diagnosed if a sCR increase ≥0.3 mg/dl in 48 hours, or ≥50% in 7 days was observed following CA/PCI.

An oral and written informed consent was given from all patients before CA/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 risk score for CIAKI[1] and CKD was staged according to guidelines criteria[13]. All available patients were assessed within a 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, re-hospitalization or renal function worsening (i.e. increased sCR or started on dialysis). Information on unavailable patients were obtained from electronic medical records or from the

referring primary care physician.

Statistical analysis

Continuous variables, presented as means and standard deviations, were compared by non-parametric 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 chi-square 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) and a two-sided significance level of <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, 1000 patients were enrolled in this prospective cohort study. Mean age was 66±11 years (range 31-88), mean baseline sCR was 1.1±0.9 mg/dl (range 0.46-10.40), and mean eGFR was 77±22 ml/min/1.73m^2 (range 4-130). Detailed baseline and clinical data are described in Table 1.

Contrast-Induced Kidney Injury: incidence and risk factors

Following CA/PCI, CIAKI was observed in 74 (7.4%) patients. Advanced age (>75 years old), compromised LVEF (<40%), CKD, ESRD on hemodialysis, diabetes, smoke, elevated CIAKI risk score (≥6), emergency CA/PCI and statins treatment correlated with CIAKI diagnosis on univariate analysis and were further evaluated with a multivariate analysis (MVA) in order to confirm their prognostic role. At the MVA only CKD, compromised LVEF, emergency CA/PCI, CIAKI risk score ≥6 and statin treatment were independent predictors of CIAKI, as showed in Table 2.

CKD was the most important risk factor for CIAKI (RR=3.61). Indeed, the 204 CKD patients had a higher incidence of CIAKI compared to 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. However, the patients

classified as stage 5 CKD had only a 25% CIAKI incidence, probably because this subgroup included 18 out of 20 patients on hemodialysis before procedure, who underwent additional dialysis session after CA/PCI.

An important CIAKI risk factor was emergency CA/PCI (RR=3.54). One-hundred ninety four (19%) patients underwent an emergency procedure, suffering a higher CIAKI incidence compared to patients who underwent a deferred/scheduled procedure: (15% versus 5%, $p<0.01$). Patients treated with an emergency procedure received larger amounts of CM (275±177 versus 223±146 ml, $p<0.01$) during longer procedures (68±33 versus 57±34 minutes, $p<0.01$) and most times without a standard pre-procedural CIAKI prophylaxis.

After a stratification for the on-admission diagnosis we saw that CIAKI occurred in 10/32 (31%) patients with decompensated heart failure, 25/164 (15%) patients with STEMI, 19/127 (15%) patients with NSTEMI, 16/379 (4%) patients with UA, 2/172 (1%) patients with instrumental signs/symptoms of myocardial ischemia and 2/126 (2%) patients with stable angina.

Statins treatment prior to CA/PCI was found to be a protective factor (RR=0.39) for CIAKI. In-hospital statin administration was continued in 555 (55%) patients already on chronic treatment (CT) while it was started on-admission (OAT) in further 152 (15%) patients. CIAKI was observed in 28/555 (5%) patients within CT subgroup and in 10/152 (7%) patients within OAT group, while it occurred in 36/293 (12%) patients not assuming statins (NST), $p<0.01$ between patients assuming statins and NST. CIAKI incidence was not significantly different comparing the CT and the OAT group ($p=0.57$). A comparison of the risk factors for CIAKI within CT, OAT and NST sub-groups is shown in Table 4. No significant baseline differences were found among these 3 statins treatment subgroups, except for a larger proportion of emergency procedures and smokers in the OAT group.

The CIAKI risk score estimated with Mehran equation had a worthy predictive value in the present study since those with a score equal or greater than 6 had a doubled risk for CIAKI (RR=2.30).

In-hospital adverse events

After CA/PCI, 17 (2%) patients died soon before discharge for cardiovascular complications. Among them, 65% had previously developed a post-procedural CIAKI, $p<0.01$. In-hospital mortality was 11/74 (15%) in patients who developed CIAKI after the index procedure versus 6/926 (0.6%) other patients (RR=26.77, 95% CI 9.6-74.8).

Long-term mortality and major adverse cardiac and cerebrovascular events

During the first year following CA/PCI, 51 patients deceased (5.1%). Those who had a CIAKI after the index procedure suffered from higher 1-year all-cause mortality rates (28% versus 3%, RR=11.83, 95% CI 6.35-22.06),

higher cardiac mortality rates (19% versus 1%, RR=17.77, 95% CI 7.87-40.11) and higher cerebrovascular mortality rates (3% versus 0.1%, RR=26, 95% CI 2.30-286.70). Over the entire 8-years follow-up period, 141 patients died. Post-procedural CIAKI was associated with an increased 8-year all-cause mortality rates (67% versus 13%, RR=14.27, 95% CI 8.30-24.55), cardiac mortality rates (40% versus 4%, RR=16.82, 95% CI 8.90-31.79) and cerebrovascular mortality rates (4% versus 0.3%, RR=13, 95% CI 2.58-65.58). The incidence of adverse events during the follow-up is described in Figure 1, while Kaplan-Meier survival curves are reported in Figure 2.

During the entire period of follow-up, an overall number of 165 MACCE were observed. Patients with CIAKI had an higher incidence of MACCE at 1-year (26% vs. 4%, RR=7.65, 95% CI 4.16-14.09) and at 8-year (56% vs. 15%, RR=6.99, 95% CI 4.09-11.94). MACCE distribution is shown in Figure 3.

Long-term renal function after a CIAKI episode

sCR was assessed at 5±2 years after discharge. A pre-post comparison of sCR values revealed an overall significant increase of sCR over time ($p<0.01$) in the entire population. Indeed, the mean sCr increase rate (CIR) was +0.06±0.25 mg/dl/year and the mean eGFR annual decrease rate (GDR) was -2.5±5.4 ml/min/1.73m^2.

Patients developing CIAKI suffered a greater and faster deterioration of renal function over time: during follow-up sCr was 2.3±2 versus 1.2±0.9 mg/dl ($p<0.01$), eGFR was 42±27 versus 68±24 ml/min/1.73m^2 ($p<0.01$), CIR was +0.23±0.41 versus +0.04±0.22 mg/dl per-year ($p<0.01$), GDR was -4.2±5.1 ml/min/1.73m^2/year versus -2.3±5.4 ml/min/1.73m^2/year ($p=0.03$).

Patients who developed CIAKI had higher proportion of CKD stage aggravation (60% versus 34%, RR=2.99, 95% CI 1.70-5.28) and higher rates of end-stage CKD evolution requiring hemodialysis (14% versus 0.5%, RR=30, 95% CI 7.72-117), compared to patients who did not show CIAKI. Among ESRD patients already on hemodialysis before the index procedure, most of them continued hemodialysis while 5 patients (28%) underwent kidney transplant during the follow-up.

Hospital readmissions after discharge

One or more hospital readmission during the 8-years of follow-up was needed for 598 (60%) patients: 358 (36%) were readmitted for cardiovascular diseases, 11 (1%) for kidney failure and 229 (23%) for other reasons. Patients with post-procedural CIAKI had higher re-hospitalization rates, especially for cardiovascular diseases: 77% vs. 58% ($p<0.01$) all-cause hospitalization, 62% vs. 34% ($p<0.01$, RR=2.4, 95% CI 1.37-4.16) cardiovascular rehospitalization,

3% vs. 1% (p=0.39, RR=2.8, 95% CI 0.60-13.34) nephrology rehospitalization, 12% vs. 24% other-cause rehospitalization (p=0.02, RR=0.44, 95% CI 0.22-0.91).

Contrast-Induced Kidney Injury: just a marker of increased cardiovascular risk or a threat itself?

To investigate the association of CIAKI with cardiovascular outcomes, an univariate analysis was carried out and the following variables show a significant correlation with the risk of developing cardiac death and/or MACCE at 8 years: advanced age, reduced LVEF, hypertension, smoke, ESRD on hemodialysis before CA/PCI, CKD, diabetes, emergency CA/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 events occurrence over time (Table 5). CIAKI was found to be the most important risk factor for 8-year cardiac death (RR=7.72) and 8-year MACCE (RR=3.72). On the contrary, statins had a powerful independent protective role over 8-year cardiac death (RR=0.43).

DISCUSSION

Contrast induced nephropathy is a well-known complication of angiographic procedures associated with lengthened hospital stay and poorer early and long term outcomes(2,3). The Mayo Clinic PCI registry study(3) showed that patients after an episode of CIAKI continued to be at higher risk of adverse events during a long-term follow-up: overall survival was lower for patients who experienced CIAKI, compared to other patients (88% vs 96% at 1 year and 55% vs 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% vs. 16%, $p<0.01$) but also with cardiac mortality (24% vs. 10%, $p<0.01$). In our study CIAKI was significantly associated with increased rates of long-term adverse events such as all-cause mortality (14-fold increased risk at 8-years, 67% versus 13%), cardiac mortality (17-fold increased risk at 8-years, 40% versus 4%), cerebrovascular mortality (13-fold increased risk at 8-years, 4% versus 0.3%) and MACCE (7-fold increased risk at 8-years, 56% vs. 15%).

These findings suggest a direct correlation between CIAKI and long-term cardiac mortality. At our opinion, some clinical considerations are needed to explain these apparently unforeseen results.

First of all, since CIAKI occurrence is influenced by several risk factors and comorbidities (i.e. compromised GFR, advanced age, reduced LVEF, diabetes and CM volume[1–3]), it is questionable whether CIAKI has a direct

effect on mortality or it 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 cases, CIAKI clinical course is transient, with sCR/eGFR values completely normalized in 5-10 days. Indeed, whether and how a transitory episode of kidney damage 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 direct 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=7.72) and MACCE (RR=3.72), independently from other concurrent but less influent factors such as advanced age, reduced LVEF, hypertension, smoke, ESRD on hemodialysis before CA/PCI, CKD, diabetes, emergency CA/PCI and elevated CIAKI risk score. This means that CIAKI is not merely a marker of increased cardiovascular risk, but it has a direct cause-effect role.

CIAKI pathogenesis involves renal tubular damage and medullary hypoxia due to CM-induced vasa recta constriction, drastically amplified by endothelial dysfunction, inflammation, and oxidative stress[15]. The consequent release of substances such as angiotensin, endothelin, TNF-alfa 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 glomerulo-tubular 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 episode of kidney injury, consistent with an increased risk of CKD progression over time. The model of "uremic memory" was hypotesized by Golestaneh et al.[19] in order to explain the long-term effects of an acute kidney injury episode. According to Zager et al [20], acute kidney injury triggers a cellular re-programming with persistent up-regulation of pro-inflammatory, pro-fibrotic and vasoconstrictive genes, culminating in progressive renal injury and extra-renal tissue injury (i.e. organ "cross-talk"). A Canadian study [21] on patients undergoing coronary angiography revealed a linear correlation between AKI severity and loss of kidney function at 3- and 12- months following the procedure. These findings are in agreement with the hypothesis stating that CIAKI may cause an accelerated CKD progression in the long-term.

In the present study CIAKI accelerated kidney function deterioration beyond the ranges of physiological aging[8], with a further statistically relevant reduction in mean eGFR in the long-term (GDR -4.2±5.1 ml/min/1.73m^2/year vs. -2.3±5.4 ml/min/1.73m^2/year, p=0.03) that is doubled in patients with CIAKI. 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 till cardiac death. Our results are in agreement with the theory of uremic memory along with previous studies that found out an association between CIAKI and long-term cardiovascular events.

In addition to the aforementioned findings it is important to notice that in this study statins administration was found to be a protective factor for CIAKI. In patients undergoing PCI, a high systemic inflammatory status is usually associated with an increased risk of periprocedural complications and cardiac events[28]. Statins are widely used in the setting of CAD because of their cholesterol lowering effect but also to improve endothelial function, to enhance atherosclerotic plaques stability, to decrease oxidative stress and inflammation (i.e. statins pleiotropic effects)[29]. Statins decrease the synthesis of endothelin, down-regulate angiotensin receptors and decrease intracellular inflammation by inhibition of NfKb and vasoconstrictor agents[30,31]. Considering CIAKI pathophysiology, statins pleiotropic effects appear to be beneficial to counterbalance CM toxicity.

The randomized placebo-controlled ARMYDA-CIN trial demonstrated that short-term pre-treatment with high dose atorvastatin can significantly decrease (RR=0.34, p=0.04) the occurrence of CIAKI in statin naïve patients with ACS receiving early PCI[32]. The study of Han et al. [33] was the first large randomized, multicenter, prospective study to evaluate the safety and efficacy of statin therapy for the prevention of CIAKI in DM patients with mild-to-moderate CKD. In this trial, it was observed that periprocedural administration of rosuvastatin 10 mg daily for a short duration (5 days) reduced the incidence of CIAKI in patients with type 2 DM and CKD, suggesting that a short course of oral statin may reduce the incidence of CIAKI after contrast medium injection in these patients. In the study by Patti et al. [34], patients receiving statins before PCI had a significant decrease of CIAKI; this early protective effect translates into better long term event-free survival. The PRATO-ACS study[35] *has shown that high dose rosuvastatin (*40 mg on admission, followed by 20 mg/day) given on admission in ACS patients scheduled for an early invasive procedure reduced CIAKI (RR=0.38, p<0.01) and 30-day adverse cardiovascular and renal events (death, dialysis, myocardial infarction, stroke, or persistent renal damage).

In the present study statins therapy was a protective factor for CIAKI at the MVA (RR=0.39 p < 0.01). Indeed, only 5% of patients on statin therapy experienced CIAKI, in contrast with 12% other patients (p<0.01). Within the statin group, there was not a significant difference among CT and OAT patients (p=0.57), meaning that statin protective effect is achieved in the periprocedural period.

Our results are in agreement with Khanal et al.[36], and Patti et al [32] in the ARMYDA-CIN supporting the prophylactic administration of statins prior to CA/PCI in order to prevent CIAKI. The latest European Society of Cardiology guidelines on myocardial revascularization advise the use of statins to prevent CI-AKI, especially in high-risk patients.

The main findings of the present study are: 1) CIAKI is independently associated with poor short- and long-term cardiovascular outcomes 2) CIAKI implies an accelerated deterioration of renal function over time 3) Statins administration greatly reduces the risk of CIAKI.

Study limitations

This study has some limitations, i.e. it is mono-centric, and therefore our observations are limited to our hospital catchment area. CA/PCI procedures in the emergency setting necessitated larger amounts of CM and this might have influenced the CIAKI rates as aforementioned. As to renal function evaluation during the follow-up, serum creatinine 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.

CONCLUSIONS

In our cohort of patients undergoing CA/PCI, a strong correlation was found between CIAKI and poor short- and long-term cardiac outcomes. Particularly, CIAKI was a predictor of increased in-hospital death, MACCE at 8 years and cardiac death at 1 and 8 years. Moreover, CIAKI caused an accelerated deterioration of renal function over time, which may explain the increased occurrence of cardiovascular events. Conversely, pre-procedural administration of statins had significantly reduced the risk of CIAKI. A careful assessment of patients at risk for CIAKI along with proper preventive measures including minimization of CM volume, use of low or iso-osmolar CM and pre-procedural hydration are of primary importance to limit the iatrogenic damage of CA/PCI procedures.

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FIGURE LEGENDS

FIGURE 1

LONG-TERM OUTCOMES OF PATIENTS WITH CONTRAST-INDUCED KIDNEY INJURY

FIGURE 2

KAPLAN-MEIER SURVIVAL CURVES IN PATIENTS WITH CIAKI

FIGURE 3

8-YEAR MAJOR-ADVERSE-CARDIAC-AND-CEREBROVASCULAR-EVENTS DISTRIBUTION