Impact of catalytic iron on mortality in patients with acute coronary syndrome exposed to iodinated radiocontrast—The Iscom Study

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Background Catalytic iron (CI) mediates vascular injury by generating reactive oxygen species. We evaluated role of CI in predicting mortality in patients with acute coronary syndrome (ACS) and studied association of contrast nephropathy with CI levels.

Methods We investigated 806 patients with ACS undergoing contrast exposure for a cardiac procedure who were followed up for 30 days.

Results Overall mortality was 1.6% at 30 days. Catalytic iron at baseline predicted mortality with CI levels significantly higher in those who died, 0.45 μmol/L (0.37, 0.68) compared with survivors 0.31 μmol/L (0.21, 0.40); $P = .004$. Catalytic iron was associated with increased risk of death in the highest quartile compared with lower 3 quartiles (hazard ratio 7.88, $P = .001$) after adjustment for age, diabetes, ST deviation, Killip class, ejection fraction, baseline creatinine, hemoglobin level, and troponin. Fifty-five patients (6.8%) developed contrast nephropathy. Patients with contrast nephropathy had a 27% increase in median CI levels from baseline up to 48 hours compared with a marginal 2.9% increase in those without contrast nephropathy (0.37, 0.14 μmol/L to 0.47, 0.20 μmol/L versus 0.35, 0.12 μmol/L to 0.36, 0.14 μmol/L, $P < .0001$). Patients with contrast nephropathy had significantly higher mortality compared with those without contrast nephropathy (9.1% vs 1.1%, $P = .001$).

Conclusion High baseline CI levels predicted mortality in patients with ACS. Occurrence of contrast nephropathy was associated with rise in CI levels and higher mortality. Therapeutic options to buffer or chelate CI may have beneficial effects on mortality in this setting. (Am Heart J 2013;165:744-51.)

Catalytic iron (CI) or labile iron is the circulating ferric iron that is nontransferrin bound and is a powerful catalyst for production of reactive oxygen species, which are mediators of cellular injury. We have previously demonstrated a significant relationship between CI and mortality in the setting of acute coronary syndrome (ACS).[1] More recently, analysis from the OPUS TIMI 16 substudy reported a relationship between increasing CI levels at baseline and all-cause mortality in the setting of ACS.[2] Iodinated radiocontrast exposure is an important cause of acute kidney injury (AKI) in patients undergoing percutaneous coronary interventions in the setting of ACS.[3,4] The risk of contrast-induced nephropathy (CIN) varies between 3% and 15% in various studies and is associated with high mortality both in the short and long terms.[5-9] The mechanism for the high mortality in patients having CIN in the setting of ACS is unclear. The present study aims to evaluate the impact of CI levels on mortality and the association of CIN and CI levels in the setting of ACS.

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http://dx.doi.org/10.1016/j.ahj.2013.02.016

Methods

Study patients

This was a multicenter study involving 6 centers across India. Patients were considered to be eligible for the study if they were older than 18 years, had presented with a clinical diagnosis of an ACS, and were posted for a cardiac catheterization involving use of at least 50 mL of iodinated radiocontrast within 72 hours of

the onset of symptoms. Criteria for exclusion were end-stage renal disease on hemodialysis, a renal transplant, fluctuation in creatinine of >0.5 mg/dL in the previous 3 months, previous contrast exposure in the previous 7 days, history of serious reactions to iodinated contrast, intake of nephrotoxic drugs within the previous 7 days, or severe concomitant disease. Written informed consent was obtained from each patient before enrollment. The study was started after approval from the ethics committees or the institutional review boards of the centers involved.

Study protocol

This was a prospective study involving 6 centers who enrolled patients with a clinical diagnosis of an ACS who were undergoing contrast exposure for a diagnostic or interventional cardiovascular procedure. Patients were identified as ACS if they presented with chest pain suggestive of myocardial ischemia or had electrocardiographic changes of ST-elevation myocardial infarction (MI) or myocardial ischemia, positive cardiac troponins, or prior history of coronary disease. The contrast agent used in most (98%) of cases was low osmolar nonionic monomeric contrast medium iohexol. The volume of contrast used was not standardized and varied between patients. None of the patients received any other measures to prevent CIN such as N acetylcysteine, sodium bicarbonate, or felodipam. The clinical follow-up visit was scheduled at 30 days. All adverse events were recorded during the 30-day follow-up period.

Serum was collected before contrast exposure (baseline sample) and at 24 and 48 hours following contrast exposure in all patients. The collected serum was immediately frozen to −70°C for storage. The serum was then sent under dry ice for analysis at the core laboratory maintaining the cold chain in transit. The core laboratory performed all the analysis. The serum was analyzed for troponin I, which was done on the chemoluminescence platform using the highly sensitive Siemens Troponin I Ultra assay (Tarrytown, NY). Serum creatinine was analyzed using the Jaffe Kinetic Method using the synchron systems creatinine reagent (CR-S) from Beckman Coulter (Fullerton, CA). We used the Beckman Coulter CX5-PRO fully automated biochemistry analyzer with isotope dilution mass spectrometry-traceable creatinine standards.

Catalytic iron was estimated using a modified bleomycin-detectable CI assay described earlier.[1,10,11] The assay is based on the fact that bleomycin in the presence of free ferric iron and a reducing agent degrades DNA. The amount of DNA degraded is directly proportional to the amount of free iron in the serum and can be quantified by the thiobarbituric acid reaction and is expressed as micromoles per liter.

The aim of the study was to study the impact of elevation in CI levels on mortality and major adverse cardiac events including reinfarction, stent thrombosis, or stroke in patients with ACS exposed to iodinated radiocontrast. *Contrast-induced nephropathy* was defined as an absolute elevation in serum creatinine of ≥0.5 mg/dL from baseline within the first 48 hours after contrast exposure. We looked at the association of CIN with CI levels in this clinical setting of ACS.

Statistical analysis

The CI levels did not follow a normal distribution pattern and so nonparametric tests were used and expressed using medians and interquartile range. Patients were divided into quartiles based on their CI concentrations at baseline and change in CI at 48 hours. Baseline characteristics were compared among quartiles using linear regression for continuous variables and log-linear analysis for categorical variables. The correlation between CI levels and other continuous baseline variables were assessed using Spearman correlation coefficient. Change in serum creatinine and CI from baseline to 48 hours are presented using median and interquartile range and the significance calculated using the nonparametric testing using the Wilcoxon rank sum test. The association between CI quartiles and clinical outcomes was analyzed using a χ^2 trend test. Cox regression analysis was used to evaluate the association between quartiles of CI and outcomes at 30 days. In multivariate logistic regression analysis, we adjusted for the effects of age, diabetes, ST deviation (>1 mm), baseline creatinine, baseline troponin, and Killip class I versus II to IV. The results are presented as odds ratio with 95% CIs.

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. We would like to thank Ms Sabina Murphy from the TIMI study group for her contribution in reviewing our statistical analysis.

Results

Study patients

Between December 2010 and October 2011, 890 patients from 6 centers were enrolled in the study. Among these, 84 patients were excluded from the analysis due to nonavailability of either the 24- or 48-hour sample. Thus, a total of 806 patients were included for the final analysis.

Of the 806 patients studied, 547 (67.9%) had ST-segment elevation MI, 199 (24.7%) had non–ST-segment elevation MI with elevated troponin I levels, and 60 (7.4%) had unstable angina.

Fifty-five patients were identified who had biochemical evidence of CIN (incidence of 6.8%). These were compared with the remaining 751 patients who did not have CIN.

The baseline demographic, clinical, and angiographic characteristics of the patients studied based on quartiles of baseline CI are shown in Table I. Higher levels of CI were associated with smoking, ST elevation MI, lower ejection fraction, higher baseline creatinine and troponin, and lower hemoglobin level. Higher levels of CI were also associated with more extensive coronary disease.

Catalytic iron levels and CIN

Baseline CI levels were identical in both the groups (0.35, 0.12 μmol/L in the group who did not get CIN and 0.37, 0.14 μmol/L in the group who developed CIN, $P = .24$). Patients who developed CIN had significant elevations in CI levels from baseline up to 48 hours

Table I. Baseline clinical and angiographic characteristics in ACS patients based on the quartiles of baseline CI

Characteristic	Total	Baseline CI quartiles (μmol/L) (median, interquartile range) Q1 (0.26, 0.07) (n = 236)	Q2 (0.33, 0.03) (n = 169)	Q3 (0.38, 0.37) (n = 200)	Q4 (0.51, 0.18) (n = 201)	*P* values for trends across quartiles
Age (y) (mean ± SD)	806	55.90 ± 11.20	57.78 ± 10.80	57.69 ± 10.28	56.12 ± 11.19	.74
Gender						
Male	652	178 (75.4%)	142 (84.0%)	165 (82.5%)	167 (83.1%)	.09
Female	154	58 (24.6%)	27 (16.0%)	35 (17.5%)	34 (16.9%)	
Weight (kg) (mean ± SD)	806	66.61 ± 8.00	66.63 ± 8.84	66.94 ± 9.78	66.35 ± 8.03	.87
BMI (kg/m^2) (mean ± SD)	806	25.01 ± 2.88	24.80 ± 3.23	24.79 ± 3.08	24.78 ± 2.92	.43
Diabetes	258	69 (29.2%)	54 (32.0%)	70 (35.0%)	65 (32.3%)	.65
Diabetes duration (y) (mean ± SEM)	258	2.97 ± 0.28	2.44 ± 0.36	2.18 ± 0.27	2.26 ± 0.31	.81
Hypertension	384	123 (52.1%)	80 (47.3%)	89 (44.5%)	92 (45.8%)	.40
Hypertension duration (y) (mean ± SEM)	384	4.18 ± 0.35	4.11 ± 0.41	3.58 ± 0.37	3.92 ± 0.38	.42
Smoking	195	60 (25.4%)	45 (26.6%)	30 (15.0%)	60 (29.9%)	.004
Stroke	14	7 (3.0%)	3 (1.8%)	2 (1.0%)	2 (1.0%)	.34
STEMI	457	131 (55.5%)	114 (67.5%)	146 (73.0%)	156 (77.6%)	<.0001
Non–ST-elevation MI	199	59 (25.0%)	49 (29.0%)	50 (25.0%)	41 (20.4%)	.30
Unstable angina	60	46 (19.5%)	6 (3.6%)	4 (2.0%)	4 (2.0%)	<.0001
Ejection fraction, % (mean ± SD)	801	46.05 ± 11.06	44.36 ± 10.37	40.16 ± 10.67	40.43 ± 10.08	.001
β-Blockers before procedure	225	68 (28.8%)	46 (27.2%)	41 (20.5%)	70 (34.8%)	.06
ACEI before procedure	101	30 (12.7%)	19 (11.2%)	34 (17.0%)	18 (9.0%)	.10
Ca-channel blockers before procedure	253	79 (33.5%)	55 (32.5%)	48 (24.0%)	71 (35.3%)	.07
Baseline creatinine (mg/dL) (mean ± SD)	806	0.95 ± 0.28	0.97 ± 0.38	0.96 ± 0.36	1.04 ± 0.40	.03
Baseline creatinine clearance (mL/min) (mean ± SD)	806	85.65 ± 30.36	84.03 ± 28.25	86.87 ± 32.99	82.05 ± 33.48	.40
Baseline troponin (ng/mL) (mean ± SEM)	806	8.75 ± 1.02	16.37 ± 1.48	19.26 ± 1.46	21.81 ± 1.44	<.0001
Hemoglobin level (g/dL) (mean ± SD)	800	13.93 ± 1.56	13.30 ± 1.69	13.12 ± 1.68	12.31 ± 1.90	.02
Volume of contrast media used (mL) (mean ± SD)	806	111.73 ± 49.74	116.32 ± 50.17	132.08 ± 63.13	113.75 ± 56.81	.17
No. of diseased vessels identified						
1	339	106 (44.1%)	70 (41.4%)	78 (39.0%)	85 (37.3%)	.005
2	262	75 (37.5%)	56 (33.1%)	64 (32.0%)	67 (22.4%)	
≥3	180	38 (24.6%)	36 (22.5%)	44 (27.0%)	62 (41.9%)	
PTCA performed	494	126 (53.4%)	106 (62.7%)	135 (67.5%)	127 (63.2%)	.045
LAD dilated	276	79 (33.5%)	61 (36.1%)	75 (37.5%)	61 (30.3%)	.46
Cx dilated	51	10 (4.2%)	12 (7.1%)	10 (5.0%)	19 (9.5%)	.12
RCA dilated	161	38 (16.1%)	30 (17.8%)	47 (23.5%)	45 (22.4%0	.17
CABG performed	29	9 (3.8%)	7 (4.1%)	6 (3.0%)	7 (3.5%)	.94

Abbreviations: *BMI*, Body mass index; *ACEI*, angiotensin-converting enzyme inhibitor; *PTCA*, percutaneous transluminal coronary angioplasty; *LAD*, left anterior descending coronary artery; *Cx*, circumflex; *RCA*, right coronary artery; *CABG*, coronary artery bypass graft.

compared with those who did not develop CIN (0.37, 0.14 μmol/L to 0.47, 0.20 μmol/L vs 0.35, 0.12 μmol/L to 0.36, 0.14 μmol/L, $P < .0001$). This 27% elevation in the CI levels in patients who developed CIN compared with a marginal increase (2.9%) in those who did not develop CIN was statistically significant ($P < .0001$) (Table II) (Figure 1).

Clinical outcomes

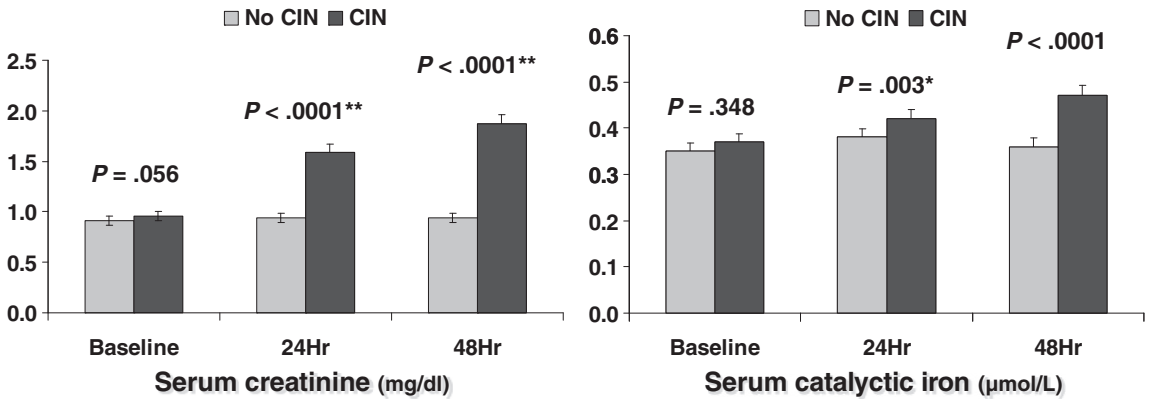
Catalytic iron at baseline predicted mortality with median CI levels significantly higher in those who died, 0.45 μmol/L (0.37, 0.68) compared with survivors 0.31 μmol/L (0.21, 0.40), $P = .004$. High baseline CI was significantly associated with mortality in the setting of ACS (Table IIIA and B) with 9 (4.7%) mortality in the highest quartile of CI compared with a mortality of 4 (0.66%) in the lower 3 quartiles combined ($P = .001$) (Figure 2). The composite end point of death, reinfarction, stent thrombosis, heart failure, or stroke was also higher in the highest quartile of CI compared with the lower 3 quartiles combined 26 (12.9%) versus 47 (7.7%) ($P = .022$).

Fifty-five patients (6.8%) developed CIN. Among the known predictors of CIN, age, diabetes, and change in CI from baseline up to 48 hours predicted the occurrence of CIN in this study (Table IV). A total of 13 adverse events (23.6%) happened in the 55 patients who developed CIN compared with 67 adverse events (8.9%) in the 751 patients who did not develop CIN ($P = .007$). Mortality was 5 (9.1%) in patients who developed CIN compared with 8 (1.1%) % in those who had no CIN ($P = .001$). Heart failure was also considerably higher in

Table II. Change in serum CI from baseline to 48 hours in patients who developed CIN and those with no CIN (median, interquartile range values) and P values (nonparametric testing by Wilcoxon rank sum test)

	Serum creatinine (mg/dL)			Serum CI (μmol/L)		
Time	**No CIN (n = 751)**	**CIN (n = 55)**	***P***	**No CIN (n = 751)**	**CIN (n = 55)**	***P***
Baseline	0.91, 0.32	0.96, 0.39	.056	0.35, 0.12	0.37, 0.14	.348
24 h	0.94, 0.33	1.59, 0.80	<.0001	0.38, 0.14	0.42, 0.20	.003
48 h	0.94, 0.32	1.87, 0.92	<.0001	0.36, 0.14	0.47, 0.20	<.0001
% Change baseline to 48 h	3.30%	94.50%	<.0001	2.90%	27.00%	<.0001

Figure 1



Comparison of the change in serum creatinine from baseline to 48 hours with the change in serum CI levels.

patients who developed CIN compared with those who did not have CIN (7 [12.7%] vs 40 [5.3%], $P = .03$). We found no difference in the rate of stroke, reinfarction, or recurrent ischemia in patients who developed CIN compared with those who did not have CIN (Table V) (Figure 2).

After adjusting for age, time from symptom onset, diabetes, ST deviation (>1 mm), ejection fraction (%), baseline creatinine, baseline troponin, hemoglobin level, and Killip class I versus II to IV, a stepwise increase in the risk of mortality persisted with increasing quartile of CI. The highest quartile of CI has a 7.9-fold increase in the risk of mortality compared with the lowest quartile ($P = .001$) (Table VI). High CI quartiles did not increase the risk of MI or heart failure. The risk of composite end point of mortality, MI, heart failure, stroke, or stent thrombosis increased marginally in the highest quartile (1.7-fold) compared with the lower 3 quartiles ($P = .04$).

Discussion

In this study, we report an association between CI measured at baseline in patients presenting with an ACS and mortality at 30 days independent of conventional risk indicators. Occurrence of CIN significantly increased the mortality risk in patients with ACS. Patients who developed CIN had significant further elevations in CI levels from baseline up to 48 hours. There was no association between baseline or change in CI levels and ischemic end points or heart failure. This relationship between raised CI levels and mortality in the setting of ACS could open new avenues for therapeutic intervention to favorably affect outcomes.

Reactive oxygen species including radicals such as superoxide free radical anion (O_2-) and hydroxyl radical ($OH-$) or nonradical reactive molecules such as hydrogen peroxide(H_2O_2) and peroxinitrite ($ONOO-$) have been the subject of intense research interest and have been implicated in various vascular and reperfusion injury syndromes.[12-14] The cellular injury induced by these reactive oxygen species is mediated by alterations of macromolecules including peroxidation of fatty acids, protein oxidation, DNA degradation (a feature used in the assay to measure CI in plasma),[15] mitochondrial depolarization, and cellular apoptosis.[16] These inherently unstable forms of reactive oxygen species are, however, extremely difficult to quantify reliably. Catalytic iron or

Table III. Adverse cardiac events by quartiles of CI at baseline (A) and comparison of first three quartiles with fourth quartile (B)

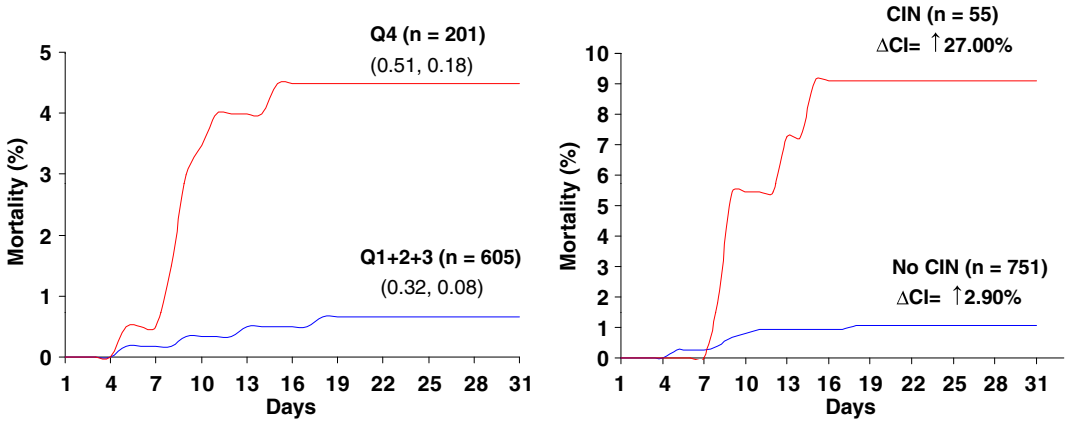
A. Adverse cardiac events by quartiles of baseline CI (CI levels expressed as medians with interquartile ranges)

Event	Quartile 1 (n = 236) (0.26, 0.07)	Quartile 2 (n = 169) (0.33, 0.03)	Quartile 3 (n = 200) (0.38, 0.37)	Quartile 4 (n = 201) (0.51, 0.18)	*P*
Mortality	1 (0.42%)	2(1.18%)	1(0.5%)	9(4.48%)	.003
Reinfarction	4(1.69%)	2(1.18%)	4(2.0%)	6(2.98%)	.547
Stent thrombosis	0(0%)	0(0%)	0(0%)	2(0.99%)	.110
Heart failure	16(6.78%)	10(5.92%)	7(3.5%)	14(6.96%)	.421
Stroke	0(0%)	0(0%)	1(0.5%)	1(0.50%)	.567
Composite	20(8.47%)	14(8.28%)	13(6.5%)	26(12.93%)	.137

B. Adverse cardiac events in the first three quartiles together compared to the fourth quartile of baseline CI (CI levels expressed as medians with interquartile range)

Event	Quartile 1 to 3 (n = 605) (0.32, 0.08)	Quartile 4 (n = 201) (0.51, 0.18)	*P*
Mortality	4 (0.66%)	9 (4.47%)	<.0001
Reinfarction	10 (1.65%)	6 (2.98%)	.241
Stent thrombosis	0 (0%)	2 (0.99%)	.014
Heart failure	33 (5.45%)	14 (6.96%)	.428
Stroke	1 (0.16%)	1 (0.49%)	.412
Composite	47 (7.76%)	26 (12.9%)	.027

Figure 2



Relationship between baseline CI levels and mortality in the 806 patients with ACS divided into the lower 3 quartiles (Q1 + 2 + 3) and the fourth quartile (Q4) and the relationship between mortality and presence or absence of CIN (ΔCI = change in CI from baseline up to 48 hours).

labile iron is that component of circulating oxidized ferric iron that is nontransferrin or ferritin bound. In circulation, this form of ferric iron is very loosely bound to albumin or citrate and is a powerful catalyst for the generation of reactive oxygen species by the Heber Weiss reaction.[10] Under normal physiologic conditions, CI is undetectable in serum due to the strong affinity of a glycoprotein called transferrin for free iron. Virtually, all the iron absorbed from the intestine or released from macrophages during red blood cell breakdown is transported in plasma as ferric iron bound to transferrin. Normally, only about one-third of the iron binding capacity of transferrin is saturated, and although the plasma half-life of transferrin is 8 to 10 days, the plasma clearance of transferrin-bound iron occurs much faster with a half-life of 60 to 90 minutes. Most of the transferrin-bound iron is delivered to the bone marrow for erythropoiesis or is used by other tissues for generating myoglobin, cytochromes, or iron-containing enzymes. The remaining enters the ferritin storage pool. This large buffering reserve capacity ensures minimal or no circulating CI is available for catalyzing the production

Table IV. Adjusted correlates of CIN in the setting of ACS

Variable	Odds ratio	95 % CIs		*P*
		Lower	Upper	
Age (y)	1.049	1.017	1.082	.003
Gender	1.038	0.519	2.078	.915
Hypertension	0.884	0.487	1.605	.685
Diabetes mellitus	2.513	1.415	4.454	.001
ST elevation MI	0.802	0.410	1.568	.519
Heart failure	0.772	0.292	2.040	.602
Ejection fraction, %	0.976	0.948	1.006	.116
Contrast volume (mL)	1.002	0.997	1.006	.528
Baseline Creatinine (mg/dL)	1.629	0.866	3.064	.130
Baseline CI (μmol/L)	1.021	0.192	5.414	.981
Change in CI (μmol/L)	3.628	1.558	8.450	.003

of the reactive oxygen species under normal physiological conditions. High levels of circulating CI can appear either due to dissociation of iron from transferrin typically with metabolic acidosis, excess recirculation of iron leading to saturation of transferrin in conditions leading to hemolysis, or bleeding or sudden release of intracellular stores of iron during periods of tissue injury.[16-21] Beyond generating reactive oxygen species, high levels of circulating CI have been demonstrated to induce thrombosis in vivo, and the iron-induced fibrous polymer is generally more resistant to fibrinolytic degradation.[22,23]

We have previously reported high levels of CI in the setting of ACS and its utility both in the early diagnosis of ACS and predicting mortality.[1] More recently in a much larger well-defined cohort of patients with ACS from the OPUS TIMI 16 study, there was a progressive stepwise increase in the mortality risk with rising levels of CI with the patients in the highest quartile of CI at an almost 4-fold increase in the mortality risk compared with baseline (hazard ratio 3.94, $P = .035$), which persisted after adjustment for traditional risk factors for mortality.[2] The present study reinforces this strong relationship between rising levels of CI at baseline and the risk of mortality in the setting of ACS.

Most patients with ACS undergo contrast exposure for either a diagnostic or therapeutic cardiac procedure. Contrast-induced nephropathy occurs in 3% to 15% of such patients and is associated with higher adverse event rates.[4] Predictors for CIN include advanced age, diabetes, heart failure, peripheral vascular disease, volume depletion, baseline renal dysfunction, and contrast volume.[8,9] The incidence of CIN leading to dialysis is low and varies between 0.5% and 2%, and in half of these, the need for dialysis is transient. The risk of dialysis-dependent AKI due to CIN in ACS varies widely depending upon several associated comorbid risk factors. The need for dialysis in the setting of CIN is, however, associated with a very high 36% in hospital mortality and an even higher 2-year mortality rate of 79%.[6] In this study of generally low-risk patients with ACS undergoing a diagnostic or therapeutic cardiovascular procedure, the incidence of CIN was 6.8%, and none of them needed dialysis.

Table V. Adverse cardiac events in patients who developed CIN and those who did not (no CIN)

Parameter	No CIN (n = 751)	CIN (n = 55)	*P*
Death	8 (1.1%)	5 (9.1%)	<.0001
Reinfarction	16 (2.1%)	0 (0.0%)	.274
Heart failure	40 (5.3%)	7 (12.7%)	.024
Stent thrombosis	1 (0.1%)	1 (1.3%)	.015
Stroke	2 (0.3%)	0 (0.0%)	.702
Composite	62 (8.3%)	11 (2.0%)	.003

The pathophysiology of CIN is not well understood, and its dramatic effect on adverse outcomes in the setting of ACS as yet unexplained.[3,5] Various mechanisms for the genesis of CIN include oxidative stress injury, alterations in glomerular blood flow with initial vasodilation followed by a more prolonged vasoconstrictor response, direct contrast toxicity to renal tubular epithelium, compliment activation, and prostaglandins. Although the incidence of contrast nephropathy is low, the occurrence of AKI secondary to contrast exposure is associated with high mortality risk both in the short and long term.[1,3] In 1 study, the in-hospital risk of mortality was 22% in patients who developed AKI compared with 1.4% in those without AKI. The 1- and 5-year mortality rates were also much higher at 12.1% and 44.6% in those with AKI compared with 3.7% and 14.5% in those without AKI.[1] In another study, 46% of the 161 patients who had AKI died at 1 year compared with 14.6% of those who did not have AKI.[3] In the present study, the mortality rate at 30 days was 9.1% in those who developed CIN compared with 1.1% in those who did not develop CIN. There was no difference in the other adverse cardiac end points such as reinfarction, stent thrombosis, or stroke, although patients who developed CIN had significantly higher incidence of heart failure.

We found significant elevations in serum CI levels from baseline up to 48 hours following contrast exposure in patients who developed CIN compared with those who did not. High baseline CI levels are associated with high mortality in the setting of ACS, and this further rise in CI levels could be one of the underlying pathophysiological mechanisms to explain the high mortality associated with CIN.

The findings of the study open important therapeutic options for the management of both CIN and mortality in the setting of ACS. The therapeutic intervention must target not only the occurrence of CIN but also address the excess mortality associated with the development of CIN in the setting of ACS. The association of CI with mortality and CIN in the setting of ACS makes it a target for potential therapeutic interventions. Reduction in iron stores has been reported to have beneficial effects on

Table VI. Unadjusted and multivariate adjusted odds ratios for 30-day clinical end points for baseline CI

	Baseline CI (Q1 + Q2 + Q3 vs Q4)					
	Unadjusted			Multivariate adjusted		
Parameter	**Odds ratio**	**95% CI**	***P***	**Odds ratio**	**95% CI**	***P***
Mortality (13)						
Q1 + Q2 + Q3 (4)	1.00			1.00		
Q4 (9)	7.04	2.15-23.13	.001	7.59	2.23-25.88	.001
MI (16)						
Q1 + Q2 + Q3 (10)	1.00			1.00		
Q4 (6)	1.83	0.65-5.10	.248	2.32	0.78-6.91	.13
Heart failure (47)						
Q1 + Q2 + Q3 (33)	1.00			1.00		
Q4 (14)	1.30	0.68-2.48	.430	1.47	0.72-2.99	.29
CIN (55)						
Q1 + Q2 + Q3 (39)	1.00			1.00		
Q4 (16)	1.26	0.69-2.30	.462	1.05	0.55-2.03	.89
Composite (73)						
Q1 + Q2 + Q3 (47)	1.00			1.00		
Q4 (26)	1.76	1.06-2.93	.049	3.10	1.34-7.17	.008

Multivariate adjustment of risk included the following variables: age, time from symptom onset, diabetes mellitus, ST deviation (>1 mm), ejection fraction (%), baseline creatinine, baseline troponin, hemoglobin level, Killip class I versus II to IV.
Composite end point included mortality, MI, heart failure, stent thrombosis, and stroke.

reperfusion injury and mortality in the setting of acute coronary interventions.[24-27] Regular phlebotomy also appears to reduce CI levels.[28] Catalytic iron levels could also be buffered in the short term with the use of plasma (a source of unbound transferrin) or with the use of iron chelators. A therapeutic trial of carefully selected patient subsets at high risk for CIN and mortality in the setting of ACS with use of oral iron chelators is needed. Clearly, more clinical evidence is necessary both to confirm our findings and to design trials to test the hypothesis.

A limitation of the study is the small number of adverse outcomes and the possibility of unrecognized confounders. The study, therefore, cannot accurately determine a causal role of CI on adverse cardiac events including mortality and CIN.

Disclosures

None of the authors have any conflict of interest to declare. There was no industry support in conducting this study.

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