Short-Term High-Dose Vitamin E to Prevent Contrast Medium–Induced Acute Kidney Injury in Patients With Chronic Kidney Disease Undergoing Elective Coronary Angiography: A Randomized Placebo-Controlled Trial

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Background—Contrast medium–induced acute kidney injury (CIAKI) is a leading cause of acquired renal impairment. The effects of antioxidants have been conflicting regarding the prevention of CIAKI. We performed a study of vitamin E use to decrease CIAKI in patients undergoing elective coronary angiography.

Methods and Results—In a placebo-controlled randomized trial at 2 centers in Iran, 300 patients with chronic kidney disease—defined as estimated glomerular filtration rate <60 mL/min per 1.73 m²—were randomized 1:1 to receive 0.9% saline infusion 12 hours prior to and after intervention combined with 600 mg vitamin E 12 hours before and 2 hours before coronary angiography or to receive placebo. The primary end point was the development of CIAKI, defined as an increase ≥0.5 mg/dL or ≥25% in serum creatinine that peaked within 72 hours. Based on an intention-to-treat analysis, CIAKI developed in 10 (6.7%) and 21 (14.1%) patients in the vitamin E and placebo groups, respectively (P=0.037). Change in white blood cell count from baseline to peak value was greater in the vitamin E group compared with the placebo group (−500 to −1500 to 200] versus 100 [−900 to 600]) (P=0.001). In multivariate analysis, vitamin E (odds ratio 0.408, 95% CI 0.170–0.982, P=0.045) and baseline Mehran score (odds ratio 1.257, 95% CI 1.007–1.569; P=0.043) predicted CIAKI.

Conclusions—Prophylactic short-term high-dose vitamin E combined with 0.9% saline infusion is superior to placebo for prevention of CIAKI in patients undergoing elective coronary angiography.


Key Words: chronic kidney disease • contrast-induced acute kidney injury • coronary angiography • vitamin E

Contrast medium–induced acute kidney injury (CIAKI) is the third most frequent cause of hospital-acquired acute kidney injury (AKI), compromising 10% of all in-hospital nephropathies and contributing to increased hospital length of stay and cost of care. CIAKI is usually defined as an absolute increase of ≥0.5 mg/dL or a relative increase of ≥25% in serum creatinine concentration within 48 to 72 hours following contrast medium exposure and may peak up to 3 to 5 days after exposure.

Several risk factors have been proposed to be associated with CIAKI, including previous renal insufficiency, diabetes mellitus, age >75 years, hypertension, congestive heart failure, volume-depleted conditions, contrast medium osmolality and volume, and nephrotoxic drugs. Pathogenesis has been linked to transient increase in renal blood flow with subsequent prolonged decrease in blood flow, necrosis of epithelial cells, medullary hypoxia, enhancement of renal vasoconstriction, and decreased activity of renal vasodilators. In addition, in experimental models, a decrease in antioxidant activity and the direct cytotoxic effect of reactive oxygen species have been shown to cause CIAKI.

To prevent CIAKI, many therapeutic strategies aimed at different pathological mechanisms have been implemented;
however, the role of different strategies is still controversial.7 Therapeutic modalities mainly include risk factor modification, hydration, diuresis, tubular alkalization, vasodilators, anti-inflammatory and antioxidant agents, and adjustment of contrast medium volume and osmolality.8–14 Vitamin E is a lipid-soluble vitamin with antioxidative and anti-inflammatory properties in the form of α-tocopherol, which has been found to be effective in the prevention and treatment of cardiovascular complications and cancer.15,16 Moreover, in some animal studies, it has been shown that vitamin E decreased cisplatin-induced oxidative damage to renal tissue17,18 and development of CIAKI.19 A clinical study showed 2 forms of vitamin E, α- and γ-tocopherol, combined with 0.9% saline infusion to be associated with a decrease in the incidence of CIAKI.20 In contrast, vitamin E plus 0.45% saline infusion before administration of contrast medium in patients with chronic kidney disease (CKD) undergoing elective computed tomography with nonionic radiocontrast agents was not protective against CIAKI on imaging evaluation.21

The purpose of the present study was to determine whether vitamin E could protect the kidneys from developing CIAKI in the setting of coronary angiography. In a prospective placebo-controlled randomized trial, for the first time, we examined the effect of high-dose preprocedural oral α-tocopherol in a cohort of CKD patients undergoing elective coronary angiography.

Methods

Study Design

In a double-blind, placebo-controlled, 2-center, randomized clinical trial, 300 consecutive CKD patients who met inclusion criteria and who underwent coronary angiography were randomized into 2 groups to receive either vitamin E or placebo from February 21, 2014, to June 13, 2015, at the Seyyed-al-Shohada Heart Center, which is a tertiary referral center, and Taleghani teaching hospital in Urmia, West Azerbaijan Province, Iran. The study was approved by the ethics committee of Urmia University of Medical Sciences. Before any study procedures were performed, consent was obtained from all participants. This study was registered at ClinicalTrials.gov (identifier NCT02070679).

All patients aged ≥18 years with baseline estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m² (based on the Modification of Diet in Renal Disease study group formula)22 who underwent coronary angiography were included in the study if they met inclusion criteria, including stable angina with ischemia and indication for coronary angiography or non–ST-segment elevation (NSTEMI) acute coronary syndrome (ACS) requiring an early invasive strategy. Exclusion criteria included acute ST-segment elevation myocardial infarction, high-risk NSTEMI warranting emerg-
some patients were willing to discharge at <72 hours, the evaluation of serum biochemistry was performed in our outpatient clinic in such cases.

Primary and Secondary End Points

The primary end point of the study was the development of CIAKI, as defined above, in the patients receiving vitamin E compared with the patients receiving placebo within 72 hours after coronary angiography.

The following outcomes were considered secondary end points: (1) changes in the levels of serum creatinine and eGFR within 72 hours after angiography; (2) postprocedure levels of complete blood cell count components, including white blood cell (WBC) count, platelet count, hemoglobin, and hematocrit; (3) changes in laboratory values from baseline to follow-up; (4) side effects of study medication; (5) hospital stay in days; (6) requirement of renal replacement therapy; (7) postprocedure ACS; (8) cerebrovascular events; and (9) in-hospital mortality.

Statistical Analysis

The purpose of the trial was to assess the effect of vitamin E on the incidence of CIAKI as the primary end point. The sample size was based on assuming 5% incidence of CIAKI in the patients receiving vitamin E and 15% in those receiving placebo. To achieve a statistical power of 80% with 2-sided α=0.05, a total of 141 patients were required in each group; 140 mL, statin use, and diabetes mellitus, as well as study site. In the logistic regression model, the CKD variable was performed using SPSS statistical software, version 21.0 (IBM Corp). Two-sided P values were calculated.

Results

Baseline Characteristics

After excluding patients who did not meet our criteria, a total of 300 patients (14.8% recruitment rate) were randomized into 2 groups. During follow-up, 298 patients (99.3%) were analyzed based on an intention-to-treat approach. The diagnosis of CIAKI was not provided during 72 hours for 3 patients in the vitamin E group and for 6 patients in the placebo group; however, results for detecting CIAKI were obtained during the fourth and fifth days after angiography, and none of these patients had CIAKI. The causes of deviation from the study protocol at follow-up are depicted in Figure 1. The clinical characteristics and biochemistry results are summarized in Tables 1 and 2. The mean age of patients was 67±11 years, and 46% of patients were male. Baseline Mehran risk score was comparable for the placebo and vitamin E groups (7.5 [IQR 5–10] and 7.35 [IQR 5.3–9.5], respectively, P=0.6). There were no statistically significant differences regarding the baseline characteristics and biochemistry results between the study groups (Table 1).

Median baseline serum creatinine concentration for all patients was 1.3 mg/dL (IQR 1.2–1.5 mg/dL). For placebo versus vitamin E, baseline serum creatinine (1.3 [IQR 1.2–1.5] versus 1.3 [IQR 1.2–1.5] mg/dL, respectively; P=0.2) and eGFR (44 [IQR 37–51] versus 45 [39–53] mL/min per 1.73 m², respectively; P=0.4) were not significantly different between groups. Comparing the placebo and vitamin E groups, serum creatinine level (1.3 [IQR 1.1–1.5] versus 1.3 [IQR 1.1–1.4] mg/dL, respectively; P=0.2) and eGFR (49 [IQR 39–55] versus 49 [IQR 41–59] mL/min per 1.73 m², respectively; P=0.2) within 72 hours were comparable. Other biochemical tests, including complete blood count components, were not significant between the study groups (Table 2).

Primary End Point

CIAKI developed in 31 (10.4%) patients across groups. Incidence of CIAKI was significantly higher in the placebo group (21 of 149, 14.1%) than in the vitamin E group (10 of 149, 6.7%; P=0.037) (Table 3). Additional definition of CIAKI (an efficacy end point) as an eGFR decrease of ≥25% over the baseline value was comparable between the study groups (13.4% for placebo versus 6.7% for vitamin E, P=0.054) (Table 3).

Secondary End Points

No side effects related to the interventions were observed. Median of hospital stay was 2 days and was comparable.
between groups (P=0.2) (Table 3). None of the study patients needed renal replacement therapy. Two cases (0.7%) of NSTE-ACS developed in the vitamin E group; however, the difference between groups was not significant (P=0.5). In the vitamin E group, 1 patient (0.35%) with acute ST-segment elevation myocardial infarction died in the hospital (Table 3).

The decrease in creatinine level was greater in the vitamin E group but not significantly. Similarly, the change in eGFR was higher in the vitamin E group but also not significantly. The median changes in serum creatinine and eGFR improved more in the placebo group, even though these patients had a higher risk of AKI compared with the vitamin E group. Furthermore, decrease in WBC count was significantly greater in the vitamin E group compared with the placebo group (Figure 2).

**Subgroup Analysis**

To compare the risk of CIAKI among patients with diabetes mellitus, we divided the patients into 2 groups according to median FBG. Among diabetic patients with FBG ≥100 mg/dL, the rate of CIAKI was significantly higher compared with those with FBG <100 mg/dL (17.4% versus 0%, respectively; P=0.044) (Table 4). Among all patients, more CIAKI developed in those with FBG ≥100 versus <100 mg/dL, regardless of study group (15.7% versus 4.8%, respectively; P=0.002) (Table 4).

We also compared the risk of CIAKI in patients with regard to history of preoperative statin use. Accordingly, the rates of CIAKI incidence in the study groups were comparable among patients with or without history of preoperative statin use and were similar to the risk of CIAKI development (Figure 3).
### Table 1. Clinical Characteristics of Patients in the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n=149)</th>
<th>Vitamin E Group (n=149)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>67±10</td>
<td>66±11</td>
<td>0.4</td>
</tr>
<tr>
<td>Male</td>
<td>69 (46.3)</td>
<td>68 (45.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.62 (1.53–1.7)</td>
<td>1.63 (1.54–1.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78 (67–83)</td>
<td>75 (67–86)</td>
<td>0.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.8 (26–32.1)</td>
<td>28.7 (25.2–32.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>102 (90–112)</td>
<td>101 (90–110)</td>
<td>0.4</td>
</tr>
<tr>
<td>Systolic BP, mm/Hg</td>
<td>130 (115–140)</td>
<td>130 (110–140)</td>
<td>0.3</td>
</tr>
<tr>
<td>Diastolic BP, mm/Hg</td>
<td>80 (70–80)</td>
<td>78 (70–80)</td>
<td>0.2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>78 (70–80)</td>
<td>78 (70–80)</td>
<td>1</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>50 (45–55)</td>
<td>50 (40–50)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>120 (80.5)</td>
<td>119 (79.9)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>53 (35.6)</td>
<td>53 (35.6)</td>
<td>1</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>25 (16.8)</td>
<td>26 (17.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>Current smoking</td>
<td>34 (22.8)</td>
<td>29 (19.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>15 (10.1)</td>
<td>7 (4.7)</td>
<td>0.076</td>
</tr>
<tr>
<td>Prior MI</td>
<td>15 (10.1)</td>
<td>18 (12.1)</td>
<td>0.5</td>
</tr>
<tr>
<td>Prior coronary stenting</td>
<td>10 (6.7)</td>
<td>9 (6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Prior cerebrovascular events</td>
<td>2 (1.3)</td>
<td>4 (2.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Metabolic syndrome*</td>
<td>82 (55)</td>
<td>75 (50.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Mehran risk score</td>
<td>7.5 (5–10)</td>
<td>7.35 (5.3–9.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>74 (49.7)</td>
<td>77 (51.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>ACEIs</td>
<td>31 (20.8)</td>
<td>37 (24.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>ARBs</td>
<td>56 (37.6)</td>
<td>54 (36.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>Statins</td>
<td>80 (53.7)</td>
<td>75 (50.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Diuretics</td>
<td>41 (27.5)</td>
<td>50 (33.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Aspirin</td>
<td>110 (73.8)</td>
<td>104 (69.8)</td>
<td>0.4</td>
</tr>
<tr>
<td>Nitrates</td>
<td>77 (51.7)</td>
<td>71 (47.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Procedural features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td>0.093</td>
</tr>
<tr>
<td>Stable IHD</td>
<td>62 (41.6)</td>
<td>48 (32.2)</td>
<td></td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>87 (58.4)</td>
<td>101 (67.8)</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>45 (30.2)</td>
<td>48 (32.2)</td>
<td>0.7</td>
</tr>
<tr>
<td>Contrast volume, mL</td>
<td>50 (50–100)</td>
<td>50 (40–100)</td>
<td>0.6</td>
</tr>
<tr>
<td>Contrast volume ≥140 mL</td>
<td>32 (21.5)</td>
<td>28 (18.8)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Table 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n=149)</th>
<th>Vitamin E Group (n=149)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline serum laboratories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>37 (32–45)</td>
<td>37 (32–45)</td>
<td>0.7</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>147 (112–191)</td>
<td>135 (103–187)</td>
<td>0.1</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>146 (120–185)</td>
<td>150 (123–180)</td>
<td>0.6</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>98 (80–130)</td>
<td>100 (81–130)</td>
<td>0.5</td>
</tr>
<tr>
<td>Blood sugar, mg/dL</td>
<td>113 (94–165)</td>
<td>122 (102–177)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD, median (interquartile range), or number (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; HDL, high-density lipoprotein; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome.

*Metabolic syndrome was detected as a criterion defined by the Third Report of the National Cholesterol Education Program.24

Patients with CIAKI had higher baseline Mehran risk scores compared with patients without CIAKI (11.3 [IQR 5.5–16.5] versus 7.5 [IQR 5.25–9.3], P=0.002). The patients with CIAKI had more metabolic syndrome (71% versus 50.6%), more congestive heart failure (16.1% versus 6.4%), higher median of baseline WBC count (8.9 [IQR 7.6–10.6] versus 7.7 [IQR 6.2–9.3]), and lower median of baseline hemoglobin (12 [IQR 9.3–12.4] versus 12.6 [IQR 11.3–13.8]). All mentioned variables were significantly different between the patients with and without CIAKI (Table 5).

The Mehran risk score groups ≤5, 6 to 10, 11 to 15, and ≥16 included 69 (23.2%), 169 (56.7%), 47 (15.8%), and 13 (4.4%) patients, respectively, and 4 (5.8%), 10 (5.9%), 7 (14.9%), and 10 (76.9%) patients in the respective Mehran risk score groups developed CIAKI (P=0.001). In the low-risk groups with Mehran risk scores ≤15, the incidence of CIAKI was lower in patients receiving vitamin E than placebo; however, for the patients with the highest risk of ≥16, no evidence showed that vitamin E was effective (Figure 4).

### Multivariable Factors for Predicting CIAKI

In the logistic regression analysis, we entered the study treatment groups, Mehran risk score as a continuous variable, metabolic syndrome, congestive heart failure, statin use, CKD, age ≥75 years, high contrast volume >140 mL, diabetes mellitus, study site, and baseline hemoglobin and WBC values as covariates in our model. The only independent predictors of CIAKI were vitamin E (odds ratio 0.408, 95% CI 0.170–0.982, P=0.045) and baseline Mehran risk score (odds ratio 1.257, 95% CI 1.007–1.569; P=0.043) (Table 5).
with CKD. Because of an increase in cardiac interventional procedures, the rate of CIAKI has steadily increased and become a leading cause of hospital-acquired AKI.\textsuperscript{4,25} The rate of complications attributable to CIAKI is high: In-hospital mortality has been found to be about 5-fold higher in patients who received contrast medium and developed CIAKI compared with those who received contrast medium but did not develop CIAKI, and 1- and 5-year mortality rates are about 4-fold higher.\textsuperscript{3,25} Despite the great impact of CIAKI in daily clinical practice, its pathophysiology is still a matter of debate. It has been speculated that contrast media exposure leads to AKI through 2 main mechanisms: cytotoxicity and higher viscosity. The cytotoxic effect of contrast media damages endothelial and tubular cells, causing decreases in nitric oxide levels and elevated oxidative stress and consequent vasoconstriction and medullary hypoxia. In addition to that effect, a decreased glomerular filtration rate and medullary

### Discussion

The key findings of the present study are that prophylactic oral administration of 1000 mg vitamin E (\(\alpha\)-tocopherol) combined with hydration of 0.9\% saline infusion appears to decrease CIAKI incidence in CKD patients undergoing elective coronary angiography compared with normal saline alone, with a number needed to treat of 13. Concordantly, the consumption of vitamin E and baseline Mehran risk scores independently predicted CIAKI incidence.

In general, contrast media are well tolerated; however, they can cause AKI, especially in high-risk patients such as those

### Table 2. Serum Values Measured at Baseline and Follow-up According to the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group* (n=149)</th>
<th>Vitamin E Group* (n=149)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.3 (1.2–1.5)</td>
<td>1.3 (1.2–1.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Serum urea, mg/dL</td>
<td>1.3 (1.1–1.5)</td>
<td>1.3 (1.1–1.4)</td>
<td>0.082</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m(^2)</td>
<td>52 (40–69)</td>
<td>48 (38–65)</td>
<td>0.2</td>
</tr>
<tr>
<td>Serum Na(^+), mEq/L</td>
<td>141 (139–143)</td>
<td>141 (140–144)</td>
<td>0.057</td>
</tr>
<tr>
<td>Serum K(^+), mEq/L</td>
<td>4.3 (3.9–4.6)</td>
<td>4.3 (4.4–4.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>WBC, (\times10^9/mL)</td>
<td>7.9 (6.26–9.7)</td>
<td>7.8 (6.5–9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Platelet count, (\times10^5/L)</td>
<td>215 (180–261)</td>
<td>205 (168–245)</td>
<td>0.077</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>39.3 (36.3–43.4)</td>
<td>39.1 (36–41.6)</td>
<td>0.4</td>
</tr>
<tr>
<td>Hemoglobin, mg/dL</td>
<td>12.8 (11.3–13.5)</td>
<td>12.3 (11.2–13.6)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

### Table 3. CIAKI Incidence and In-Hospital Outcomes in the Study Groups

<table>
<thead>
<tr>
<th>CIAKI definitions</th>
<th>Placebo Group (n=149)</th>
<th>Vitamin E Group (n=149)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine increase by (\geq 25%)</td>
<td>21 (14.1)</td>
<td>10 (6.7)</td>
<td>0.037</td>
</tr>
<tr>
<td>Serum creatinine increase by (\geq 0.5) mg/dL</td>
<td>20 (13.4)</td>
<td>8 (5.4)</td>
<td>0.017</td>
</tr>
<tr>
<td>Serum creatinine increase by (\geq 25%) or Serum creatinine increase by (\geq 0.5) mg/dL</td>
<td>21 (14.1)</td>
<td>10 (6.7)</td>
<td>0.037</td>
</tr>
<tr>
<td>eGFR decrease by (\geq 25%)</td>
<td>20 (13.4)</td>
<td>10 (6.7)</td>
<td>0.054</td>
</tr>
</tbody>
</table>

### In-hospital outcomes

- Medication side effect: 0 (0) vs 0 (0); \(P=1\)
- Hospital stay, day: 2 (2–3) vs 2 (2–3); \(P=0.2\)
- Renal replacement therapy: 0 (0) vs 0 (0); \(P=1\)
- NSTE-ACS: 0 (0) vs 2 (1.4); \(P=0.5\)
- AMI: 0 (0) vs 1 (0.7); \(P=1\)
- Cerebrovascular events: 0 (0) vs 0 (0); \(P=1\)
- Death: 0 (0) vs 0 (0.7); \(P=1\)

Values are presented as number (%). \(P<0.05\) is considered statistically significant. Values are presented as median (interquartile range). eGFR indicates estimated glomerular filtration rate; WBC, white blood cell.

*Values were not provided for 6 and 3 patients during 72 hours in the placebo and vitamin E groups, respectively.
hypoperfusion develop that are attributable to the exponential increase in tubular fluid viscosity.\(^{26}\)

Many risk factors have been reported to be associated with CIAKI after coronary interventions and can predict patients at risk for CIAKI.\(^{27}\) The important factors include calculated creatinine clearance, diabetic status, and contrast media volume prior to a proposed coronary intervention.\(^{2}\) For better risk stratification, some risk scores have been useful; the Mehran risk score is a simple and widely used tool.\(^{28}\) It is based on the presence of 8 factors (hypotension, use of an intra-aortic balloon pump, congestive heart failure, CKD, diabetes, age >75 years, anemia, and volume of contrast). In our study, we found that metabolic syndrome, congestive heart failure, and elevated WBC count and decreased hemoglobin at baseline were associated with CIAKI. Despite relationships between these factors and CIAKI in univariate analysis, these effects disappeared in multivariate analysis. Nevertheless, baseline Mehran score directly predicted CIAKI incidence with an odds ratio of 1.257 (95% CI 1.007–1.569, \(P=0.043\)). Individual risk factors did not predict CIAKI, but the predictive role of the Mehran score demonstrated that these factors can be used for risk stratification. We think that the relatively small sample size of our cohort, despite being sufficiently powered to detect primary outcome of interest, might be the main obstacle to showing the individual impact of risk factors on the incidence of CIAKI.

CIAKI was detected mainly by biomarkers, which are dependent on underlying diseases. Consequently, the results of one study cannot be generalizable to another study under different settings. In such a situation, finding the proper
A diagnostic tool for early detection of AKI may be of great importance in clinical trials. The measurements of serum creatinine and urine output are considered the primary tools for diagnosing AKI in daily practice because use of biomarkers with unproven reliability might result in incorrect interpretation of clinical trials. Despite the shortcomings of serum creatinine to estimate GFR, with very few exceptions, it is the only diagnostic marker used in clinical trials for CIAKI. The absolute change in serum creatinine within 48 to 72 hours after contrast medium exposure has been routinely used as a definition of CIAKI, as in our study; we defined CIAKI as an absolute increase ≥0.5 mg/dL or a 25% relative increase in the baseline serum creatinine concentrations measured within 72 hours after intervention. The serum creatinine concentration has been shown to peak within 2 to 3 days after exposure, although the majority of studies have reported serum levels at 48 hours, which can underestimate the incidence of CIAKI or underpower studies. We believe that in daily practice, serum creatinine is a simple, inexpensive, and available marker until a new biomarker is proven beneficial for such circumstances.

The preventive strategies are focused on the possible pathophysiological mechanisms involved in CIAKI. Increase in tubular viscosity and resultant decrease in urine flow rate lead to diminishing GFR by activation of the renin-angiotensin system. Hydration therapy has been demonstrated to be the main preventive strategy by increasing tubular urine flow and consequently diminishing contrast medium concentration and viscosity of tubular lumens. Furthermore, contrast media

**Table 5. Predictors of CIAKI According to Univariate and Multivariate Analyses**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With CIAKI (n=31)</td>
<td>Without CIAKI (n=267)</td>
</tr>
<tr>
<td>Vitamin E (vs placebo)</td>
<td>6.7% vs 14.1%</td>
<td>93.3% vs 85.9%</td>
</tr>
<tr>
<td>Mehran risk score</td>
<td>11.3 (5.5–16.5)</td>
<td>7.5 (5.25–9.3)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>22 (71)</td>
<td>135 (50.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5 (16.1)</td>
<td>17 (6.4)</td>
</tr>
<tr>
<td>Baseline WBC count, ×10^9/mL</td>
<td>8.9 (7.6–10.6)</td>
<td>7.7 (6.2–9.3)</td>
</tr>
<tr>
<td>Baseline hemoglobin, mg/dL</td>
<td>12 (9.3–12.4)</td>
<td>12.6 (11.3–13.8)</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%). AMI indicates acute myocardial infarction; CIAKI, contrast medium–induced acute kidney injury; OR, odds ratio, WBC, white blood cell.

*Only factors that predicted CIAKI are reported.
lead to generation of reactive oxygen species, which may lead
to vasoconstriction, and hypoperfusion of the medulla,
promoting mitochondrial generation of reactive oxygen
species. Accordingly, use of antioxidants (eg, vitamin C,
N-acetylcysteine, vitamin E) represents an effective strategy
to prevent CIAKI, considering their roles in attenuating the
oxidative damage from radiocontrast.

A protective effect of oral vitamin C against CIAKI was
found in a cohort of CKD patients undergoing coronary
angiography or intervention. Furthermore, a recent meta-
analysis revealed conflicting results regarding the efficacy of
N-acetylcysteine infusion against CIAKI. In contrast, studies
of vitamin E have been associated with inconsistent findings.
Kitzler et al demonstrated that intravenous vitamin E in
addition to 0.45% saline infusion was not effective against
CIAKI in CKD patients undergoing computed tomography
scanning compared with 0.45% saline infusion alone. In
another study, however, α- or γ-tocopherol combined with
administration of 0.9% saline resulted in a decrease in CIAKI
after elective coronary angiography. Vitamin E protects
against oxidative damage by stabilizing cell membranes and
scavenging lipid peroxyl radicals; therefore, it is able to break
peroxyl chain propagation reactions. The antioxidant activity
of vitamin C is mediated by direct effects on hydroxyl radicals
and hydrogen peroxide to reduce lipid peroxidation. Moreover,
N-acetylcysteine, a glutathione precursor, has been found to enhance intracellular glutathione levels, as detoxi-
fying hydroxyl groups, in rats but not in human studies.
Given these different mechanisms of action among antioxi-
dants, further studies are required to establish a more robust
conclusion about their effects in clinical practice, especially
for prevention of CIAKI.

Statins are antilipid agents with anti-inflammatory action in
cardiovascular disease and have been used for the prevention
of CIAKI. A recently published meta-analysis showed that
preprocedure statin therapy reduced the risk of CIAKI
compared with control groups; however, patients with CKD
stage ≥3 were largely underrepresented in published studies,
and statin therapy did not significantly decrease CIAKI
development in trials that enrolled patients with eGFR <60 mL/min per 1.73 m². The authors concluded that further
trials were required to better define the role of statins for
protection against CIAKI in the setting of coronary angio-
ography, particularly in patients with CKD stage ≥3. Moreover, in
another meta-analysis, Lee et al found that short-term high-
dose statin (≥40 mg atorvastatin) significantly reduced the
incidence of CIAKI compared with low-dose statin or placebo
in patients undergoing coronary angiography. In our study,
we were unable to show the benefits of statin use beyond the
study intervention. We think that the main limitation of this
study in this regard was the small sample size to detect statin
effects. We also did not prescribe a high-dose statin
preprocedurally for our cohort, and that dose can have more
impact than a low-dose statin, as demonstrated previously.

The glycemic status of patients has been found to
influence renal protection of patients on exposure to contrast
medium. Patients with elevated FBG are at higher risk of
developing CIAKI than nondiabetic patients. The main
biomarkers indicating glycemic status are FBG, blood sugar,
and hemoglobin A1c levels. Among patients undergoing
coronary catheterization, elevated baseline hemoglobin A1c,
but not blood sugar, was also associated with increased risk
of CIAKI in nondiabetic patients. In contrast, another study
showed that elevated preprocedural blood glucose correlated
with greater risk for CIAKI in nondiabetic patients undergoing
coronary angiography. In addition, Yoshikawa et al found
that hemoglobin A1c ≥6.5% was associated with changes in
renal function after contrast exposure on computed tomog-
raphy angiography. In line with the mentioned findings, we
also demonstrated that CIAKI incidence was significantly
higher in patients with elevated preprocedural FBG, and CIAKI
developed more often in those who also had diabetes
mellitus. We did not measure other markers indicating
nephropathy in diabetic patients, especially hemoglobin A1c
and albuminuria, which have been shown to be associated
with the risk of CIAKI in diabetic patients.

In our study, the patients who developed CIAKI had higher
peak levels of WBCs, representing the possible role of
inflammation in the setting of CIAKI; WBC count is a marker
for acute inflammation. Interestingly, we found that WBC
change from baseline to its peak value within 72 hours was
significantly greater in the patients receiving vitamin E
compared with those receiving placebo. These findings
confirm that inflammatory mechanisms may be involved in
the pathogenesis of CIAKI incidence. It may be speculated
that the effects of vitamin E are applied, in some part, through
attenuation of inflammation in addition to scavenging free
oxygen radicals. A recent meta-analysis that evaluated the
effects of vitamin E–coated dialyzer on oxidative status and
inflammation revealed that dialyzer membrane containing
vitamin E decreased inflammatory markers, reflecting the
anti-inflammatory property of vitamin E.

Limitations
In interpreting these data, some limitations should be
considered. First, the results of this study cannot be extended
to very high-risk patients, particularly those who need to
undergo renal replacement therapy, because the number of
patients with a Mehran score ≥16 was insufficient and no
patients needed dialysis during our study. Second, we did not
measure cystatin C level, which seems to be a more reliable
marker than serum creatinine. Moreover, we used the
Modification of Diet in Renal Disease formula to calculate
eGFR. Nonetheless, these limitations are observed in most of the previous clinical trials in this setting. Third, we did not measure the serum levels of vitamin E at baseline and follow-up to evaluate the effect of patients’ vitamin E status on our findings. Fourth, 2 patients developed NSTE-ACS, and 1 patient had acute ST-segment elevation myocardial infarction and died during hospitalization; all of these events occurred in the vitamin E group. Because of the low numbers of events and very short-term follow-up, we were unable to assess why these events happened in the vitamin E group. Finally, changes in WBC levels were used to show the probable anti-inflammatory role of vitamin E, whereas C-reactive protein could be a more accurate biomarker than WBCs for demonstrating such an effect in the prevention of the CIAKI.

Conclusion

The results of this study showed that pretreatment 1000 mg vitamin E (α-tocopherol) combined with 0.9% saline infusion is a safe, well-tolerated, efficacious, and readily available antioxidant to prevent CIAKI incidence in moderate- to high-risk CKD patients undergoing elective coronary angiography.

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Disclosures

None.

References

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Short-Term High-Dose Vitamin E to Prevent Contrast Medium–Induced Acute Kidney Injury in Patients With Chronic Kidney Disease Undergoing Elective Coronary Angiography: A Randomized Placebo–Controlled Trial

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