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Novel Biomarkers of Contrast-Induced Kidney Injury after Endovascular Procedures: An Interventional Cardiologists Notion

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Abstract

Modern achievements of interventional cardiology in treatment of coronary heart disease (CHD) have significantly increased frequency of interventions and volume of contrast media (CM). Contrast-induced acute kidney injury (CIAKI) associated with CM administration is determined by 26.5 μmol/l increase in serum creatinine (SCr) within 48 - 72 hours or > 1.5-fold SCr increase versus its known or estimated level in the previous 7 days. Without effective disease management, prevention with early CIAKI risk stratification and cessation of nephrotoxic medications taken by patients are important. Given significant complexity in existing CIAKI treatment, modern therapeutic options are limited only to adequate renal injury prevention. The problem's significance and diagnostic limitations associated with SCr definition require search for clinically and diagnostically significant AKI biomarkers. In terms of coronarography and percutaneous coronary interventions, several studies have been conducted on clinical and diagnostic significance of some biomarkers. This article characterizes and discloses prospective practical use of neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP), kidney injury molecule-1 (KIM-1), cystatin C (CysC) and interleukins-6,8,18 (IL-6,8,18) in interventional cardiology.

Keywords

Percutaneous Coronary Intervention, Acute Kidney Injury, Coronary Artery Disease

1. Introduction

Modern achievements of interventional cardiology in treatment of coronary artery disease (CAD) have significantly increased frequency of performed interventions and, consequently, volume of administered contrast media (CM). As a number of patients receiving endovascular care and CM consumption increase yearly, contrast-induced acute kidney injury (CIAKI) incidence increases accordingly [1] [2]. CIAKI is an iatrogenic complication of intravascular CM administration, meeting one of the following AKI criteria: 26.5 μmol/l of serum creatinine (SCr) increase within 48 - 72 h or > 1.5-fold SCr increase versus its known or estimated level in the previous 7 days [3]. Direct AKI develops within the first 12 - 24 h after an interventional procedure and statistically increases hospitalization duration, complications incidence, mortality and associated hospital costs [2] [4]. Despite toxic CM effects on the renal tubule epithelium, no safe replacement has yet been found. Given significant complexity in existing CIAKI treatment, modern therapeutic options are limited only to adequate renal injury prevention.

CIAKI pathophysiology is under active study. Damage mechanisms include vasoconstriction, oxidative stress and direct cytotoxic CM effect [5] [6] [7]. CM causes endothelin release and violates local prostaglandin regulation, resulting in persistent renal vasoconstriction [8]. Subsequent filtration pressure drop reduces tubular current speed, increases CM residence time in the tubules, thus contributing to their toxic interaction with the epithelium. Combination of oxidative stress with inflammation leads to nephron mass damage and death, thus resulting in AKI (**Figure 1**). Fortunately, in most CIAKI cases, renal malfunction is transient, with full recovery within 3 - 5 days [9].

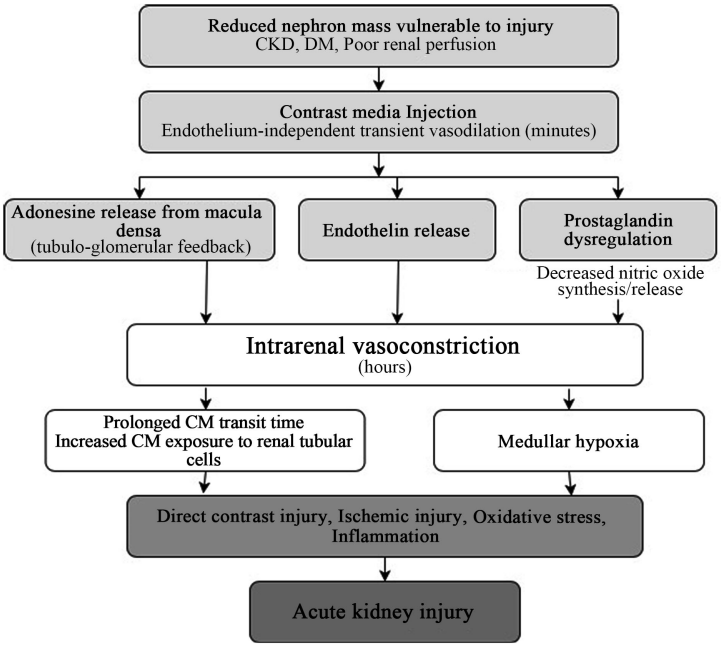

Figure 1. CIAKI development. CKD (chronic kidney disease), DM (diabetes mellitus), CM (contrast media).

The strongest CIAKI risk factor is initial CKD. Other independent predictors are age (CIAKI risk 15% higher in patients over 65), diabetic nephropathy, peripheral artery disease, heart failure and use of non-ionic CM [10] [11] [12]. Demographic shift towards the elderly population, along with increasing incidence of diabetes mellitus (DM) with concomitant CKD and CAD, prioritizes early CIAKI detection and prevention [13].

CIAKI incidence in the Russian Federation is 5% - 8% of total patient population undergoing radiographic contrast studies (RCS) and doubles in patients with interventional CAD procedures history [1] [13]. After percutaneous coronary interventions (PCI), patients have the highest AKI risk due to higher CM volume administered [2] [14] [15] [16].

Incidence of severe AKI requiring renal replacement therapy is about 1%, but mortality in this cohort is significant 36%, with depressing 2-year survival rate of 20% [17] [18] [19]. CIAKI impact on mortality in non-dialysis cohorts is also high—22% versus 1.4% in non-CIAKI patients, with 1 and 5-year survival rates of 88% versus 96% and 55% versus 85%, respectively [17] [18] [19]. CIAKI presence affects hospitalization duration, with 74% probability of re-hospitalization for heart failure decompensation [4] [18] [20] [21].

As mentioned above, therapeutic effects on possible CM cytotoxicity mechanisms, renal vasoconstriction and free radical damage are limited to preventive measures—primarily risk stratification, optimal CM selection and intravenous hydration. Consensus on optimal hydration mode has so far been reached only for saline solution and sodium bicarbonate [22] [23] [24] [25].

Under the practical guidelines of the European Society of Urogenital Radiology (ESUR), Kidney Disease Improving Global Outcomes (KDIGO, 2012) guidelines, European Renal Association—European Dialysis and Transplant Association, European Renal Best Practice (ERA-EDTA ERBP) consensus paper to the KDIGO 2012 guidelines and clinical guidelines by the Scientific Society of Russian Nephrologists (SSRN), there are some common key points in CIAKI prevention [26]-[30] (**Table 1**).

1) Mandatory CIAKI risk stratification and kidney disease screening to all candidates for radiographic contrast study by measuring SCr level or completing a questionnaire with CIAKI risk identification (DM, CAD, CKD).

2) Saline solution and sodium bicarbonate have comparable efficacy in preventive hydration.

Table 1. Assessment of evidence quality (under KDIGO clinical guidelines).

Evidence quality	Value
A—high	Experts believe expectation effect is close to estimated effect.
B—medium	Experts assume expectation effect is close to estimated effect but might also differ significantly.
C—low	Expectation effect might differ significantly from estimated effect.
D—negligible	Expectation effect is very amphibolic and might differ significantly from estimated effect.

3) Oral hydration as the only CIAKI prevention method is not recommended.

4) For intra-arterial CM injection, 1.4% sodium bicarbonate solution 3 ml/kg/hour an hour before intervention or 0.9% sodium chloride solution 3 - 4 h before and 4 - 6 h after CM administration is recommended.

5) In case of severe heart failure NYHA (Class III-IV) or end-stage renal failure (GFR below 15 ml/min/1.73 m^2), prehydration is calculated individually.

6) Hemodialysis and hemofiltration for preventive CM removal in patients at high CI-AKI risk are non-effective (2C).

7) Low doses of dopamine (1A), fenoldopam (1C), atrial natriuretic peptide (1C), adenosine antagonists (2C), calcium channel blockers (1C), loop diuretics (1B) and mannitol (1B) are not recommended for CIAKI prevention.

8) Patients on hemodialysis, with end-stage renal failure and anuria, may be given intra-arterial CM injection without risk of additional renal injury (1A).

Based on the above recommendations, the best CI-AKI prevention is risk stratification and adequate intravenous or oral hydration, although the latter's role remains in doubt in a number of studies. Brar S. *et al.* suggested modifying intravenous hydration mode by invasive control of left ventricular end-diastolic pressure (EDP). 396 patients were divided into 2 cohorts: with EDP control (196 patients) and without (200 patients). The cohort without control was assigned standard hydration protocol of 1.5 ml/kg/h intravenously, and the EDP control cohort was subdivided: the subgroup with EDP below 13 mmHg was given 5 ml/kg/h, with EDP at 13 - 18 mmHg - 3 ml/kg/h and with EDP above 18 mmHg - 1.5 ml/kg/h. Hydration was conducted before CM administration, during the procedure and for 4 hours afterwards. SCr was measured on the procedure day and twice from the 1st to the 4th day afterwards. As a result, CIAKI incidence was lower in the invasive EDP control cohort (6.7%) versus the cohort without EDP control (16.3%) - HR 0.41 (95% CI 0.22 - 0.79, p = 0.005). The researcher group concluded that intravenous hydration under invasive EDP control is a safe and effective CIAKI prevention in patients planned for coronary angiography (CAG) and PCI [31].

On the other hand, a major prospective randomized study AMACING did not show superiority of preventive intravenous hydration over no prevention at all. 660 patients with planned RCS were randomized into 2 cohorts: one given intravenous hydration with 0.9% sodium chloride solution (328 patients) and another without prevention. The result was no difference in CIAKI incidence in the 2 cohorts, and no-prevention strategy was recognized cost-effective versus intravenous hydration strategy [32].

In the absence of effective disease management, it is critical to withdraw nephrotoxic medications taken by patients in advance. These include non-steroidal anti-inflammatory, antifungal, antiviral, antitumor mediactions, as well as immunosuppressants and antibiotics, especially aminoglycosides. For DM patients, metformin is cancelled 48 h before and limited 48 h after CM administration. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ACB), due to their possible harm and insufficient data on their positive

effects on renal hemodynamics and GFR, should be excluded from therapy 1 day before the study [28] [33].

For optimal CM selection, preference should be given to isoosmolar CM (IOCM, e.g. iodixanol). Several studies have confirmed CIAKI incidence drop in IOCM cohorts versus low-osmolar CM (LOCM, e.g. iohexol) [17] [34]. In meta-analysis of 16 randomized studies involving 2727 patients, McCullough *et al.* revealed statistically lower CIAKI incidence in IOCM cohorts [35]. This work was supported by similar meta-analysis of 17 studies with 1365 patients in total [36]. RCS must involve baseline CM amount for administration to achieve optimal results [4] [19] [37] [38].

No pharmacologic agent has shown statistically significant efficiency in CIAKI prevention, according to multiple studies. The most frequently studied agent is N-acetylcysteine (NAC). A major 3-year multicentre study of 90,578 patients showed no difference neither in CIAKI incidence (5.5% vs. 5.5%, $p = 0.99$) nor in mortality (0.6% vs. 0.8%, $p = 0.69$) [39]. Several meta-analyses have confirmed no clinically significant NAC effect on CIAKI incidence [28] [33].

The problem's significance and diagnostic limitations associated with SCr require search for a new clinically and diagnostically significant AKI biomarkers.

2. Biomarkers

For adequate diagnosis of end-organ damage, the "ideal biomarker" must be highly sensitive and specific. Marker level must proportionally reflect cellular damage and be identified as early as possible after CM administration. Biomarker concentration monitoring must be reproducible in all subsequent studies. If the agent's noci-influence on the target organ is stopped, marker concentration must immediately fall. The problem of using SCr as a renal injury biomarker is that SCr level raised by CM administration characterizes GFR decrease already in place rather than acute cellular damage. SCr growth is observed only 48 - 72 h after CM administration [40]. SCr concentration itself depends on many factors: age, sex, muscle mass, metabolic rate, hydration degree and some medications. Given increased outpatient PCI and practice of early hospital discharge after PCI, early AKI detection and prognostic assessment using new biomarkers is a promising research area.

Recent consensus on biomarker use in clinical practice highlights diversity of their routine use to stratify risk, diagnose, determine injury cause and predict CIAKI outcome. Determination of marker combination concentration statistically improves quality of medical care for CIAKI patients due to early diagnosis, risk stratification and early preventive and curative interventions [41] [42].

In terms of coronary angiography and PCI, several studies have been conducted on clinical and diagnostic significance of some AKI markers. In this article, we will try to characterize several markers potentially significant for application:

1) NGAL;

2) L-FABP;

3) KIM-1;
4) CysC;
5) IL-6,8 and 18.

3. NGAL/Lipocalin-2

NGAL—a protease-resistant polypeptide linked to gelatinase enzyme in specific neutrophil granules. NGAL is synthesized and expressed by cells under stress, involved in apoptosis processes, bacterial growth suppression and inflammation modulation. In the kidneys, NGAL participates in mechanisms of recovery after ischemic injury, regulates renal iron transport, differentiation processes in renal tubular epithelial cells and is involved in transport of lipophilic substances such as vitamin E and arachidonic acid [43].

NGAL is mainly synthesized in the distal nephron and excreted in the urine after renal injury [44]. Serum NGAL accumulating profusely during AKI is also scarcely secreted in activated neutrophils, as part of systemic inflammatory response, and in various body tissues (liver, lungs, colon). The latter property limits the prognostic use of serum NGAL due to competing AKI and systemic inflammatory response in biomarker identification [43].

NGAL concentration measurement for CIAKI detection after diagnostic coronary angiography or PCI was evaluated in patients with and without proven CKD. Potential significance of identification of NGAL as an early CIAKI biomarker was revealed in a study involving 100 patients with normal baseline SCr undergone PCI. CIAKI incidence was 11% and serum NGAL was significantly increased in 2 ($p < 0.05$) and 4 hours ($p < 0.01$) after PCI and urine NGAL significantly increased after 4 ($p < 0.05$) and 8 hours ($p < 0.001$). As a result, serum NGAL after 2 hours and urine NGAL concentrations after 4 hours were independent variables of CIAKI development over the next 48 hours [45].

Malyszko *et al.* have analysed patients with DM and normal initial renal function [46]. In cohorts with and without DM, CIAKI incidence was the same (14% and 10% respectively, $p = 0.67$), whereas serum NGAL concentrations in the DM cohort after 2 ($p < 0.05$), 4 ($p < 0.01$) and 8 hours ($p < 0.01$) were significantly higher. Noteworthy, both serum NGAL and urine NGAL reactions were faster than other known CIAKI biomarkers (CysC, KIM-1, IL-18, L-FABP), whereas increased serum and urine NGAL values persisted in CIAKI patients for 48 hours after CM administration, versus non-AKI patients.

Bachorzewska-Gajewska *et al.* have studied NGAL concentrations in 25 patients without DM and with normal SCr after PCI. Significant increases in serum and urine NGAL concentrations were found in 2 and 4 hours respectively, while maintaining high concentrations up to 48 hours after PCI, despite no SCr dynamics [47]. In another study, serum NGAL concentration was evaluated 24 hours after diagnostic angiography (8.7% CIAKI incidence) to become significantly higher than in patients without clinically significant CIAKI [48].

A study by Qureshi *et al.* has detected no significant difference in serum and

urine NGAL concentrations soon after PCI and in 24 hours in CKD patients [49]. Table 2 summarizes major NGAL studies in CIAKI.

4. L-FABP

Liver fatty acid-binding protein (L-FABP) is synthesized extensively in tissues involved in fatty acid metabolism. 2 types are identified—liver and heart (L-FABP, H-FABP). H-FABP has been extensively studied for myocardial ischemia in acute coronary syndrome and its use in CIAKI is currently limited. However, L-FABP is also localized in the cell cytoplasm of proximal renal tubules. L-FABP selectively binds to free cytoplasmic fatty acids and lipid peroxidation products in anoxic cellular damage [50]. Although higher L-FABP levels may accompany minor renal injury, L-FABP is a specific renal injury marker [51] [52].

One study of patients after PCI revealed early L-FABP response to AKI, with marker concentration increasing in 4 hours ($p < 0.001$) and remaining elevated for 48 hours ($p < 0.001$) after intervention [47]. The findings, however, were not confirmed by Malyszko *et al.* showing higher L-FABP levels in CIAKI patients only in 24 hours [46].

Manabe *et al.* have examined patients with stable CKD and completed angiography [53]. L-FABP concentrations were evaluated before, 24 and 48 hours after intervention. Independent CIAKI variables were baseline L-FABP (>24.5 pg/g), initially higher SCr, ejection fraction below 40% and chronic ACE inhibitors usage. Serum L-FABP a day ($p = 0.014$) and two ($p = 0.003$) after the procedure was significantly higher in the cohort with developed CIAKI. Test sensitivity and specificity were 82% and 69% respectively ($p = 0.002$) at 8.6% AKI incidence.

Table 2. NGAL studies.

Number of patients	Patient characteristics	CIAKI incidence, %	Marker capture time, h	Conclusion	Statistics	Authors
100	GFR > 60 ml, Age 63.2 ± 12.0 yrs.	11%	0, 2, 4, 8, 24	Significant NGAL increase in 2 hours	Serum NGAL increase in 2 hours ($p < 0.05$), in 4 h ($p < 0.01$), in 8 hours ($p < 0.05$), urine NGAL increase in 4 hours ($p < 0.05$), in 8 hours ($p < 0.001$), in 12 hours ($p < 0.05$)	[45]
140	DM/non-DM, GFR > 60 ml, Age 63.8 ± 11.4 yrs.	14% (DM) 10% (non-DM)	0, 2, 4, 8, 24	Significant NGAL increase in both cohorts, more significant in DM cohort	$p < 0.05$ for both cohorts vs marker level before CM administration, $p < 0.001$ for DM vs non-DM cohort	[46]
25	non-DM, GFR > 60 ml, Age 64.3 ± 9.8 yrs.	0%	0, 2, 4, 12	No CIAKI. Significant NGAL increase in 2 hours	Serum NGAL increase in 2 hours ($p < 0.05$), in 4 hours ($p < 0.01$), urine NGAL increase in 4 and 12 hours ($p < 0.05$)	[47]
150	GFR > 60 ml, Age 66.3 ± 9.9 yrs.	8.7%	0.24	Significant NGAL increase during first 24 hours	$p < 0.05$ vs. control group	[48]
208	DM + GFR > 60 ml, Age 70.8 ± 8.5 yrs.	18.8%	0, 2, 4, 12 - 24	Significant NGAL increase already in 2 hours	$p = 0.03$ (2 hours), $p = 0.007$ (4 hours), $p = 0.0015$ (12 - 24 hours)	[49]

The 2 research groups found similar regularity with L-FABP concentration increase 1 and 2 days after routine angiography with and without PCI. 14 days after procedure, given SCr recovery in AKI cohort patients, L-FABP concentration remained increased, whereas concentration in the non-AKI cohort was normal [54] [55].

5. KIM-1

Kidney injury molecule-1 (KIM-1)—a transmembrane glycoprotein involved in T-helper lymphocyte differentiation. Biomarker is from immunoglobulin superfamily and not expressed in healthy renal cells. KIM-1 strengthens in response to ischemia, nephrotoxic medications, acute/chronic kidney transplant malfunction and in CKD due to synthesis in proximal nephrons [56] [57] [58] [59]. KIM-1 pathophysiological role in CIAKI is most probably associated with dedifferentiation and reduction of tubule cell residues, subsequent tubular obstruction and phagocytosis of necrotic and apoptotic cell residues.

Malyszko *et al.* studied changed KIM-1 concentration in 140 patients after angiography and found that marker concentration increase reveals itself only 24 ($p < 0.05$) and 48 hours ($p < 0.05$) after CM administration, yielding in diagnostic significance to NGAL and IL-18 [46]. To date, KIM-1 has hardly been studied in terms of CIAKI after PCI.

6. CysC

CysC is an endogenous cysteine-proteinase inhibitor synthesized in all nucleated cells. The biomarker is filtered through the glomerular membrane and reabsorbed in kidneys. CysC is a key to intracellular catabolism of various peptides and proteins. CysC is produced and released into plasma in relatively constant amount, has no binding protein, is 99% filtered by the renal glomerulus and not secreted by proximal renal tubules [57] [60] [61] [62]. Its level does not depend on race, age, sex, muscle mass, infection, hepatic disease, inflammation or glucocorticosteroid intake [63].

Patients developing CIAKI after angiography had higher baseline CysC (1.36 ± 0.28 mg/l vs. 1.08 ± 0.22, $p = 0.007$), thus proving hypothesis about initial impact of renal malfunction on AKI risk after CAG/PCI [55]. Based on the described characteristics, CysC is a potentially promising AKI biomarker.

7. IL-6

Interleukin-6 (IL-6)—a pleotropic cytokine with both pro- and anti-inflammatory properties. IL-6 is secreted extensively by endothelial cells in response to proinflammatory signals including hypoxia, tissue damage, internal organ dysfunction and synthesis of tumour necrosis factor-α (TNF-α). In target cells, IL-6 binds to IL-6R receptor directly activating gp130 and leading to activation of Jak/STAT signal pathway, followed by STAT3 activation. IL-6R distribution is limited to hepatocytes, monocyte and neutrophil subpopulations, as well as some T-and

B-lymphocyte populations.

No studies have yet evaluated linkage of higher IL-6 concentration to CIAKI in patients with acute coronary syndrome (ACS) or stable coronary artery disease (SCAD).

8. IL-8

Interleukin-8 (IL-8 or chemotactic factor) has primary functions in triggering chemotaxis and migration of neutrophils, lymphocytes, macrophages and granulocytes to infection and inflammation sites. Cytokine is secreted by any cells with Toll-like receptors involved in innate immune response. Both IL-8 monomer and dimer activate CXCR1 and CXCR2 receptors as chemokine lymphocyte agents.

Data on IL-8 linkage to AKI are scarce. One study showed strong correlation of urine IL-8 level with continued renal allograft dysfunction due to the reperfusion injury [64]. IL-8 plasma levels over time may predict AKI development in septic patients, whereas high IL-8 plasma levels were death predictors for seriously ill AKI patients [64].

No studies have yet evaluated linkage of higher IL-8 concentration to CIAKI in ACS or CAD patients.

9. IL-18

Interleukin-18 (IL-18)—a proinflammatory cytokine secreted by tubular epithelial cells. IL-18 is a neutrophil-independent biomarker, activated by intracellular cysteine proteinases and caspases-1. Activated cytokine is further excreted by the cell and, after activation in proximal tubules, enters interstitial space and urine [65].

Ling *et al.* evaluated IL-18 in 150 patients after CAG. 13 patients (8.7%) developed CIAKI. IL-18 level was higher in CAG group 24 hours after the procedure (area under the curve (AUC)—0.75, $p = 0.011$, OR 10.7). IL-18 level 24 hours after CM administration was also found to be an independent variable of a long-term major cardiovascular events (HR 2.09, $p < 0.01$) [48].

Malyszko *et al.* found IL-18 increase 2 hours after the angiography ($p < 0.05$), with maximum concentration at 24 hours ($p < 0.01$) [46]. A study by He *et al.* has contrarily revealed no statistical difference in IL-18 levels in CIAKI and non-CIAKI cohorts 24 and 72 hours after CM administration ($p < 0.05$), at 9.5% CIAKI incidence [66].

10. Biomarker Combination

AKI biomarker combinability is a promising topic for detailed study. Endre *et al.* noticed scarce relevant publications, whereas difficulties in finding clinical significance of identifying single biomarker panel were due to wide marker combinability [42]. In theory, combination of several markers representing different AKI mechanisms is essential in CIAKI diagnosis.

Use of a preformed panel of certain biomarkers may increase sensitivity and AUC of early CIAKI diagnosis. As Han *et al.* (54) have found, combination of NGAL, KIM-1 and NAG (N-acetyl-β-D-glucosaminidase) improves AUC to detect AKI up to 0.80 when taking markers immediately and up to 0.84 when taken 3 h after the cardiac surgery. In this combination, biomarkers showed better AKI detection results than any single marker.

Acceptability of this approach in AKI diagnosis has also been proved by a study comparing predictive CysC value after elective cardiac surgery. Identification of only CysC showed 71% sensitivity and 92% specificity, whereas combination of NGAL, CysC, IL-18, NAG and retinol-binding protein (RBP) demonstrated better sensitivity and specificity results (93% and 92% respectively) with AUC 0.98 ($p < 0.001$) [67].

11. Conclusion

Without early diagnosis and prevention, CIAKI leads to higher cardiovascular morbidity, extended admission, rare but significant need for renal replacement therapy and involves 5-fold rise of in-hospital mortality [2] [15]. Iatrogenic and predictable CIAKI nature makes early diagnosis of CIAKI crucial. Certain AKI biomarkers have proved their efficacy in several studies, but detailed studies of their combinability are necessary to improve the quality of medical care for patients with performed PCI [19] [55] [62] [68].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviation

CHD: Coronary heart disease
CM: Contrast media
CIAKI: Contrast-induced acute kidney injury
SCr: Serum creatinine
NGAL: Neutrophil gelatinase-associated lipocalin
L-FABP: Liver-type fatty acid binding protein
CysC: Cystatin C
IL-6,8,18: Interleukins-6,8,18
CKD: Chronic kidney disease
DM: Diabetes mellitus
RCS: Radiographic contrast studies
PCI: Percutaneous coronary intervention
ESUR: European society of urogenital radiology
KDIGO: Kidney Disease Improving Global Outcomes
ERA: European Renal Association
EDTA: European Dialysis and Transplant Association
ERBP: European Renal Best Practice
SSRN: Scientific Society of Russian Nephrologists
EDP: End-diastolic pressure
CAG: Coronary angiography
KIM-1: Kidney injury molecule-1
ACS: Acute coronary syndrome
SCAD: Stable coronary artery disease
NAG: N-acetyl-β-D-glucosaminidase
RBP: Retinol-binding protein