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Acute Kidney Injury in Patients with ST-Elevation Myocardial Infarction

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Abstract

Acute kidney injury (AKI) is an important issue in patients hospitalized with ST-elevation acute myocardial infarction (STEMI). Thisrenal complication has a complex and multifactorial pathogenesis and, depending on the definition used, its incidence ranges between 5% and 30%. In STEMI patients, the development of AKI, as well as its severity, have been independently associated with strikingly higher morbidity and mortality, both at short-term and long-term follow-up.

The purpose of the present review is to provide a framework of reference and updates on the currently available evidence of AKI in STEMI. Raising cardiologists' awareness of the clinical and prognostic impact of AKI might ultimately improve the outcomes of STEMI patients.

Keywords: Acute kidney injury; ST-elevation myocardial infarction; Primary percutaneous coronary intervention, Prognosis

Introduction

The overall survival of patients with ST-elevation myocardial infarction (STEMI) has significantly improved during the past two decades, due to the combined use of novel pharmacologic therapies and aggressive revascularization strategies [1]. The interest of cardiologists is now shifting towards subsets of patients whose mortality still remains very high, thus contributing to the overall mortality of STEMI. Those developing acute kidney injury (AKI) represent a critical example of STEMI patients associated with a poor prognosis.

A growing amount of data confirms the clinical and prognostic relevance of AKI in this clinical setting. However, it is worth noting that the current guidelines on the management of STEMI patients do not focus much attention on AKI [2]. Surprisingly, while recommendations exist for the management of rare STEMI-associated complications, such as mitral valve rupture or Dressler pericarditis, no clear indications are provided on the management of this frequent complication. Indeed, The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) Adding Insult to Injury AKI Study reported, in 2009, that only 50% of patients who died with AKI in different clinical contexts received good care [3]. Therefore, in this review, we aim at providing a framework of reference for raising awareness of AKI in the cardiology community, with the goal to improve the outcomes of STEMI patients with AKI.

Definition of AKI

Acute kidney injury is characterized by sudden impairment of kidney function, ranging from a minimal elevation in serum creatinine (sCr) to anuric renal failure requiring a temporary renal replacement therapy (RRT) [4]. To date, the literature includes more than 30 definitions of AKI [5]. In order to overcome heterogeneous definitions of AKI, three newer classification systems have been developed [6-8] (Table 1). The first that was graded in increasing levels of severity was the RIFLE classification (Risk, Injury, Failure, Loss, and End-stage kidney disease) [6]. In 2005, Chertow "et al." [9] showed that increases in sCr level as small as 0.3 mg/dL are highly associated with patients' outcomes. Accordingly, the Acute Kidney Injury Network (AKIN) criteria for AKI were developed [7]. Finally, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Work Group developed the third and most recent classification [8].

The incidence of AKI and its prognostic implications, as assessed by RIFLE and KDIGO criteria, were compared in 1,050 patients with acute myocardial infarction (AMI) [10]. Patients who were diagnosed with AKI by KDIGO, but were missed by RIFLE criteria, had a significantly longer hospitalization and a significantly higher adjusted hazard ratio for 30-day and 1-year mortality,

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Table 1: Main current classifications of acute kidney injury.

RIFLE	
	an acute ↑ in sCr over 7 days
Risk	↑ in sCr ≥1.5 x baseline
Injury	↑ in sCr ≥2.0 x baseline
Failure	↑ in sCr ≥3.0 x baseline or ↑ in sCr ≥0.5 mg/dL if baseline sCr ≥4.0 mg/dL
Loss	Complete loss of kidney function >4 weeks
ESRD	End-stage renal disease >3 months
AKIN	
	an acute ↑ in sCr within 48h
Stage 1	↑ in sCr ≥1.5-2.0 x baseline or ↑ in sCr ≥0.3 mg/dL
Stage 2	↑ in sCr >2.0-3.0 x baseline
Stage 3	↑ in sCr >3.0 x baseline or sCr ≥4.0 mg/dL with an acute ↑ ≥0.5 mg/dL or initiation of RRT
KDIGO	
	an acute ↑ in sCr within 48h
Stage 1	↑ in sCr ≥1.5-1.9 x baseline or ↑ in sCr ≥0.3 mg/dL
Stage 2	↑ in sCr ≥2.0-2.9 x baseline
Stage 3	↑ in sCr ≥3.0 x baseline or sCr ≥4.0 mg/dL with an acute ↑ ≥0.5 mg/dL or initiation of RRT

AKIN=acute kidney injury network; ESKD=end-stage kidney disease; KDIGO=Kidney Disease: Improving Global Outcomes; RIFLE= Risk, Injury, Failure, Loss, and End-stage renal disease; RRT=renal replacement therapy; sCr=serum creatinine.
↑=increase; ↓=decrease.

suggesting that the KDIGO criteria are more suitable for AKI diagnosis in AMI. We recently demonstrated that, in STEMI patients undergoing primary percutaneous coronary intervention (PCI), AKI, defined as a >0.5 mg/dL sCr increase, provides the best in-hospital mortality risk stratification when compared to other definitions, namely >0.3 mg/dl increase and >25% increase [11].

In STEMI patients, once the occurrence of AKI is recognized and its severity graded, an additional issue should be taken into account. The definition of AKI is based on the relative increase in sCr level compared to baseline value. In STEMI, sCr at hospital admission is usually used as the reference value; however, it cannot be considered a true baseline value because an acute hemodynamic impairment may have already increased it. As a result, the incidence of AKI, as well as its severity, may be underestimated in STEMI. This was confirmed by a recent study in which 1 out of 10 patients hospitalized with AMI showed a decrease (>0.3 mg/dL) in sCr during their stay at the Coronary Care Unit. Notably, their in-hospital mortality was 4-fold higher than that of patients with stable renal function (2% vs. 0.5%) [12]. Therefore, the apparent renal function improvement after hospital admission possibly reflects the recovery phase of a transient AKI started before hospitalization.

Incidence of AKI in Stemi

After initial reports in old cohorts of STEMI patients [13,14], Sadeghi "et al." [15] were the first to demonstrate the clinical relevance of AKI in more contemporary STEMI patients undergoing primary PCI. They evaluated the incidence of AKI, defined as an absolute sCr increase >0.5 mg/dl, in 1,884 patients enrolled in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. This renal complication occurred in 4.6% of patients, and it was associated with a strikingly worse prognosis. The incidence of AKI, however, was probably underestimated in this study. Indeed, patients with cardiogenic shock and renal insufficiency (sCr>2 mg/dl), the two most important predictors of AKI in STEMI patients, were excluded from this trial, and daily creatinine measurement was not routinely performed. More recent data from the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry, a nationwide sample of 59,970 patients with AMI, demonstrated that AKI occurred in 16% of patients. Similarly, in our cohort of 3,210 patients with AMI (53% with STEMI), AKI developed in 13% of patients (64% with AKIN stage 1 and 36% with AKIN stage 2-3), while RRT was required in 20% of AKI patients [16]. In another report including STEMI patients undergoing primary PCI only, AKI occurred in 19% of patients [17]. These data were recently confirmed in the large-scale Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial [18], which documented that AKI occurred in 16% of the study population. Notably, in patients with STEMI complicated by cardiogenic shock, this figure increased up to 50%, with 25% of them requiring RRT [19].

Pathophysiology of AKI in Stemi

In STEMI patients, AKI is a complex phenomenon preconditioned by underlying renal dysfunction and modulated by multiple contributing factors, which go beyond the mere exposure to a large volume of contrast agent during primary PCI [20]. Accordingly, in a cohort of >1,000 STEMI patients, Goldberg "et al." [21] demonstrated that 22% of AKI patients only underwent primary PCI. In addition to the well-known recognized link between high contrast volume and AKI development in STEMI [18,20], the most crucial mechanism causing AKI includes hemodynamic changes due to reduced cardiac output, ultimately decreasing GFR. Of note, factors reflecting cardiocirculatory impairment, such as reduced left ventricular ejection fraction, left anterior descending culprit lesion, and high end-diastolic pulmonary arterial blood pressure, are independently associated with AKI in STEMI [22]. Furthermore, changes in volume status, medical therapies, athero-embolism (during PCI or intra-aortic balloon pump insertion), and bleeding, are involved in the pathogenesis of AKI. Additionally, a burst inflammatory kidney

Table 2: Predictive models for acute kidney injury development.

Mehran score
• age >75 years
• hypotension
• congestive heart failure
• intra-aortic balloon pump
• serum creatinine
• diabetes mellitus
• anemia
• volume of contrast media
Marenzi score
• age >75 years
• anterior STEMI
• time-to-reperfusion >6 hours
• contrast volume >300 mL
• intra-aortic balloon pump
Andò score
• age
• leftventricularejectionfraction
• estimatedglomerularfiltration rate

damage has been advocated among the potential causes [23-25]. In 141 STEMI patients, enhanced inflammatory response, increased oxidative stress, and activation of the sympathetic nervous system synergistically accelerated the development of AKI, causing a vicious cycle amplifying the progression of the ongoing renal injury [26]. Finally, metabolic factors, including acidosis and acute hyperglycemia, may favor the development of AKI [27-29].

Contrast agent volume and type

Among the modifiable risk factors, careful attention to contrast volume is a key factor, especially in high-risk patients. In this regard, it is worth noting that some of the key pathophysiologic factors typically associated with STEMI and involved in the development of AKI, such as hypoxia, acidosis, hypotension, hyperglycemia, and dehydration, by causing vasoconstriction, may all aggravate the renal damage related to contrast administration. The negative impact of a high contrast volume on AKI has also been widely recognized in STEMI [18,30]. In particular, formulating a ratio of maximum contrast dose is attractive to interventional cardiologists, allowing for a target to be set before, or during, primary PCI. Indeed, we showed that, in STEMI patients who received a greater contrast volume than the maximal contrast dose, estimated by the simple Cigarroa's formula (5 x body weight [kg]/sCr [mg/dl]), the incidence of AKI increased dramatically [31]. A contrast ratio≥1, obtained by dividing the administered contrast amount by the calculated maximal contrast dose, was associated with a 3-fold higher incidence of AKI, compared with a contrast ratio <1 (45% vs. 13%) (31). Moreover, a contrast ratio ≥1 was associated with a nearly 20-fold higher incidence of RRT use (9% vs. 0.5%). More recently, Gurm "et al." [32] proposed the ratio of contrast volume to the calculated creatinine clearance as a tool to reduce the risk of AKI in patients undergoing PCI, also in the setting of primary PCI. Taken together, these data suggest the use of the minimal amount of contrast to achieve optimal intra-procedural out comes in high-risk STEMI patients. Finally, differently from what occurs in elective diagnostic and procedural settings, where iso-osmolar agent exposure is associated with a lower risk of AKI when compared to some types of low-osmolar contrast media [33,34], in STEMI patients, contrast osmolality seems to play only a marginal role. This evidence derives from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction (CONTRAST-AMI) trial, where AKI incidence after primary PCI was similar in patients receiving iopromide and iodixanol contrast media [35]. This result was then confirmed in the HORIZONS-AMI sub-study, which showed no association between AKI and type of contrast used (low-osmolar vs. iso-osmolar) [18].

Predictive Models of AKI in Stemi

One important issue in STEMI is the possibility to early identify patients who will develop AKI. Several risk factors for AKI have been recognized: some are associated with pre-existing kidney vulnerability (chronic kidney disease [CKD], advanced age, diabetes) [30], some are due to the clinical condition (hypoxia, anemia, heart failure, hemodynamic instability, acute hyperglycemia, neurohormonal activation), and some are directly due to the toxicity of contrast media. These factors have been integrated into risk scores to identify patients at high risk of AKI [17,36,37] (Table 2).

The Mehran score was developed in 2004 to predict AKI after non-urgent PCI, and it includes eight clinical and procedural variables [36]. Recently, Wi "et al." [30] retrospectively evaluated the Mehran score in 1,041 AMI patients; they found a higher score in patients with AKI than in those without AKI (9.4±6.8 vs. 5.4±4.9). Accordingly, Sgura "et al." [38] showed that this score is a good predictor of major cardiovascular and cerebrovascular events in STEMI patients. We also demonstrated, in STEMI patients undergoing primary PCI, that the combination of 5 variables, easy to collect in the initial hours of hospital stay, independently predicted AKI [17]. Using these variables, a risk score was developed: AKI incidence ranged from 4% when no risk factor was present to 100% when 4-5 factors were present. Of note, the in-hospital mortality rate revealed a significant gradation as the risk score increased. Both Mehran's risk score and ours were validated in the large HORIZONS-AMI trial [18] (Figure 1). Finally, Andò "et al." [37], recently proposed a new score based on three simple clinical parameters; at logistic regression analysis, for each 1-point increase in this score, a 5-fold increase in AKI was observed.

Prognosis Associated with AKI

Acute kidney injury in STEMI has been consistently associated with a worse outcome, and namely with strikingly higher short-term and long-term mortality rates [26,39-41]. Its development and severity have been independently associated with increasing morbidity and mortality, length of hospital stay, risk of progression to end-stage renal disease (ESRD), and subsequent hospitalization for cardiovascular and renal events [38,39,42,43]. Moreover, it has been suggested that a particular threshold for sCr increase may not exist and that there is a continuous rise in mortality risk in parallel with the magnitude of sCr changes [44,45]. Finally, there is growing awareness of long-term renal consequences after an AKI episode, which may include persistent loss of kidney function with development of CKD [46-49]. This probably accounts for the higher long-term mortality observed in STEMI patients experiencing AKI. Interestingly, the worse renal prognosis seems to involve also patients with a full recovery of sCr values. Therefore, AMI patients with transient or sustained AKI should be carefully followed up after discharge, with the aim of slowing CKD progression to ESRD.

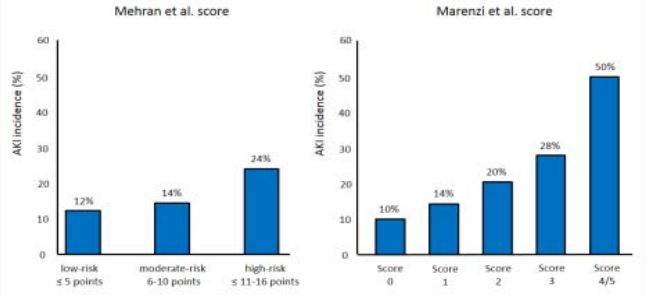

Figure 1: Incidence of acute kidney injury (AKI) observed in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) clinical trial according to the Mehran and Marenziscores for AKI prediction.

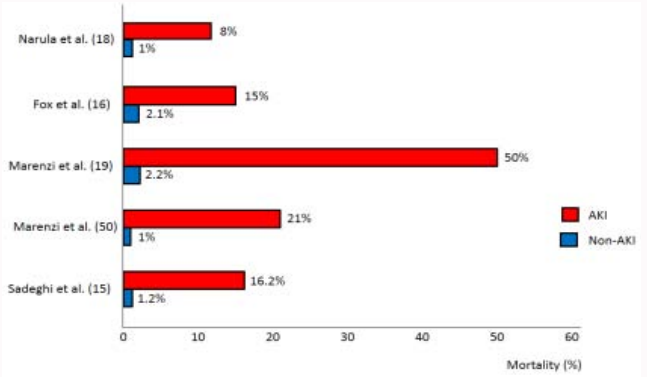

Figure 2: In-hospital mortality rates of ST-elevation myocardial infarction patients with and without acute kidney injury (AKI) observed in main clinical studies.

Short-term prognosis

Figure 2 In the CADILLAC trial, 30-day mortality was 16% in patients with AKI, as compared to 1% in those without AKI [15]. In our cohort of 3,210 AMI patients (50% with STEMI), a significant progressive increase in hospital mortality was observed going from patients with no AKI to those with stage 1 AKI and to those with stage 2-3 AKI (1%, 9.5%, 43%, respectively) [50]. Goldberg "et al." [21] reported a similar association, with an 11.4-fold higher mortality risk in STEMI patients developing AKI. Such an increased risk was also confirmed at 6-month follow-up [21]. In a very-high-risk setting, such as the case of STEMI complicated by cardiogenic shock, AKI was found to be the strongest independent predictor of in-hospital mortality (relative risk 12.3), occurring in 50% of AKI patients, and in 62% of those requiring RRT [19].

More recently, Fox "et al." [16] complemented these findings in a substantially larger population, showing an increased in-hospital mortality rate in patients with mild (0.3-<0.5 mg/dL), moderate (0.5-<1.0 mg/dL), and severe (≥1.0 mg/dL) AKI (6.6%, 14.2%, and 31.8%, respectively), compared to those without AKI (2.1%).

Recent interest has been focused on the detrimental association between AKI and bleeding. Bleeding risk progressively increases with lower GFR [51], and an association between bleeding and short-term and long-term mortality has been documented also in STEMI [52-54]. In a retrospective registry enrolling 1,346AMI patients, AKI was likely to occur in those with major bleeding (OR=2); on the other hand, AKI patients had significantly higher rates of major bleeding (11% vs. 4%) and blood transfusions than those without AKI.

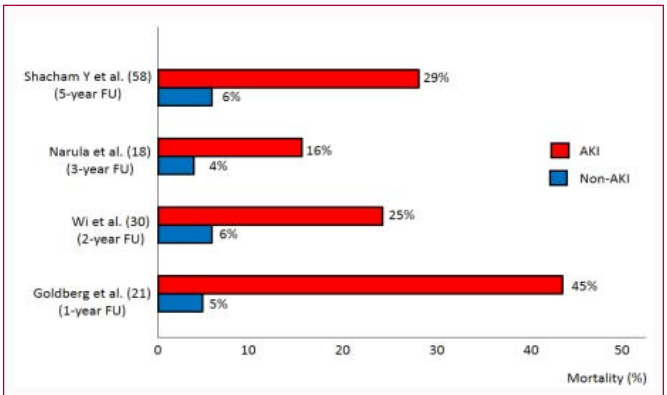

Figure 3: Long-term mortality rates of ST-elevation myocardial infarction patients with and without acute kidney injury (AKI) observed in main clinical studies. FU=Follow-up.

Finally, in the study by Fox "et al." [16], in-hospital major bleeding rate ranged from 8.4% (no AKI) to 32.7% (severe AKI). Plausible explanations for this association may include abnormal platelet function in patients with CKD combined with their inhibition by antiplatelet agents, in addition to potential overdosing errors for renally cleared antithrombotic agents. Thus, anticoagulant therapy in STEMI should be daily evaluated in order to early detect AKI and to promptly adequate dosage according to renal function changes.

Long-term prognosis

A recent meta-analysis of 48 studies evaluating long-term outcomes after AKI suggested that AKI of any severity, regardless of the investigated clinical setting, is associated with a doubled long-term mortality risk [55]; interestingly, risk adjustment for post-discharge GFR only modestly attenuated this estimate [56].

The first systematic description of AKI-related worse outcomes at long-term follow-up in AMI was provided by Newsome "et al." [46]. In their nationally representative sample of 87,094 Medicare beneficiaries discharged after AMI, they demonstrated an independent association between sCr level increases during hospitalization and subsequent long-term risk of both ESRD and mortality. These risks were manifested over 10 years of follow-up; they were evident for even small increases in sCr, as low as 0.1 mg/dL, and present in a dose-response manner [46]. In 2005, Goldberg "et al." [21] demonstrated that an sCr rise >0.5 mg/dL following AMI was associated with a marked increase in 1-year mortality. In 2011, Hwang "et al." [57] showed that the 1-year mortality of STEMI patients without AKI was 4%, while it was 25%, 43%, and 89% in those with stage 1, 2, and 3 AKI, respectively. In the study by Wi [30], AKI onset following primary PCI was independently associated with a significant increase in the 2-year cumulative event rate of death or dialysis.

When the investigation was extended to longer follow-ups, data still consistently showed the close relationship between AKI and worse prognosis in STEMI [18,40,57]. Indeed, Narula "et al." [18] found that STEMI patients with AKI had an 8% mortality rate at 30 days and a 16% mortality rate at 3 years, as compared to 0.9% and 4.5% mortality rates at 30 days and 3 years in patients without AKI, respectively. Finally, Shacham "et al." [58] have recently extended this observation up to a 5-year follow-up. Taken together, these data concur to support the long-term adverse prognostic impact of AKI in STEMI (Figure 3).

Conclusion

Acute kidney injury is a frequent complication of STEMI and a strong independent predictor of short-term and long-term cardiovascular and renal outcomes and mortality. Despite much progress and increased recognition of AKI in this setting, it still remains an underestimated clinical condition. Therefore, additional efforts are needed in order to define evidence-based therapeutic strategies, both during the acute phase of the disease and later at follow-up, aiming at improving overall outcomes in STEMI patients.

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