Cardiovascular Drugs and Therapy (2018) 32:81–98
https://doi.org/10.1007/s10557-017-6766-6

REVIEW ARTICLE

The Incidence and the Prognostic Impact of Acute Kidney Injury in Acute Myocardial Infarction Patients: Current Preventive Strategies

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Published online: 19 January 2018

Abstract
Acute kidney injury (AKI) is one of the most common complications during hospitalization in various clinical settings. The goal of this review was to assess the incidence of AKI in acute myocardial infarction patients (AMI), how this incidence is affected by the diverse definitions, and if there is variability in the reported rates over recent years. Additionally, we sought to appraise the impact of AKI on short- and long-term prognosis of these patients. Finally, we report on the current preventive measures as they are suggested in the current guidelines of various societies, we comment on the evidence that support them, and we review the literature for other proposed therapeutic strategies, which either failed to prove their efficacy or they are not adequately confirmed yet. Due to the heterogeneity in AKI definition and in the population studied of the published data, the incidence of AKI ranged from 5.2 to 59%. A recent meta-analysis reported a median value of 15.8%. All studies assessing AKI-related prognosis in AMI patients suggested that presence of AKI has detrimental effect on patients prognosis, raising mortality two- to threefold not only during the 30 first days but also during the first year after the acute event. Various treatment modalities have been proposed for prevention of AKI in AMI patients; however, the majority of them failed to prove their efficacy in the clinical trial arena. Hydration, use of iso- or low-osmolar agents at the lowest possible dose during coronary interventions, and use of statins have been proposed among others. Nonetheless, the prevalence of AKI after an AMI still remains high today and therefore it is crucial for the practicing physician to be aware of its presence and for the scientific community to identify novel measures for a more efficacious prevention.

Keywords Acute kidney injury · Acute myocardial infarction · Kidney function · Prognosis · Incidence

Introduction

It is known that acute kidney injury (AKI) is one of the most frequent complications during hospitalization of a patient, with detrimental effects on his prognosis in a variety of clinical scenarios including abdominal aortic aneurysm repair surgery [1], coronary angiography [2], cardiopulmonary bypass surgery [3], and critically ill patients in the intensive care unit [4]. Furthermore, recent evidence suggested a strong correlation between cardiac and kidney function, which engendered the term "cardiorenal syndrome" in the heart failure and in the acute coronary syndrome (ACS) setting [5]. Within this context, it is reasonable to assess the incidence and also the prognosis of AKI in patients with acute myocardial infarction (AMI).

A fair amount of research endeavored to answer the aforementioned query. However, one of the major problems one has to encounter when assessing the accumulated data is the heterogeneity in the definition of AKI, as more than 30 proposed terms were in use until the last decade [6]. In 2004, Acute Dialysis Quality Initiative (ADQI) developed the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria, which was the first attempt to reach a consensus [7]. In 2007, the Acute Kidney Injury Network (AKIN) published the AKIN criteria [8], and finally in 2012, the Kidney Disease Improving Global Outcomes (KDIGO) released their criteria which build off of the RIFLE criteria and the AKIN criteria [9]. The result is that there are at least three incumbent definitions and classifications for AKI (Table 1), not considering the contrast-induced nephropathy definition,

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Table 1 Definitions of acute kidney injury

Definitions of acute kidney injury		
Acute Dialysis Quality Initiative, RIFLE Criteria		
Stage	Renal function criteria	Urine output criteria
Risk	sCr increased 1.5–2 times baseline or GFR decreased > 25%	UO < 0.5 mL/kg/h > 6 h
Injury	sCr increased 2–3 times baseline or GFR decreased > 50%	UO < 0.5 mL/kg/h > 12 h
Failure	sCr increased > 3 times baseline or GFR decreased 75% or SCr ≥ 4 mg/dL; acute rise ≥ 0.5 mg/dL	UO < 0.3 mL/kg/h > 12 h (oliguria) or anuria for 12 h
Loss of function	Persistent acute renal failure: complete loss of kidney function > 4 weeks (requiring dialysis)	
ESRD	Complete loss of kidney function > 3 months (requiring dialysis)	
Acute Kidney Injury Network, AKIN Criteria		
1	sCr increase 1.5–2 times baseline or ≥ 0.3 mg/dL increase	UO < 0.5 mL/kg/h > 6 h
2	sCr increase 2–3 times baseline	UO < 0.5 mL/kg/h > 12 h
3	sCr increase ≥ 3 times to baseline or increase to ≥ 4 mg/dL with an acute increase of 0.5 mg/dL or on renal replacement therapy	UO < 0.3 mL/kg/h > 12 h (oliguria) or anuria for 12 h
Kidney Disease: Improving Global Outcome, KDIGO Criteria		
1	sCr 1.5–1.9 times baseline or ≥ 0.3 mg/dL increase	< 0.5 mL/kg/h for 6 h
2	sCr 2–2.9 times baseline	< 0.5 mL/kg/h for 12 h
3	sCr ≥ 3 times baseline or increase in serum creatinine to ≥ 4 mg/dL or initiation of renal replacement therapy	< 0.3 mL/kg/h for 24 h or anuria for ≥ 12 h

The RIFLE criteria are defined as changes within 7 days, while the AKIN criteria suggest using 48 h. KDIGO criteria are defined as absolute changes within 48 h or as relative changes within 7 days

AKIN Acute Kidney Injury Network, *ESRD* end-stage renal disease, *GFR* glomerular filtration rate, *KDIGO* Kidney Disease Improving Global Outcomes, *RIFLE* Risk, Injury, Failure, Loss and End-stage kidney disease, *sCr* serum creatinine, *UO* urine output

ensuing in studies a lack of homogeneity, and hobbling the efforts to extract solid conclusions about the pathophysiology and the epidemiology of the disease.

Apart from assessing the incidence of AKI and its associated prognosis in patients with AMI, the identification of the preventive measures which can inhibit the occurrence of this detrimental complication is also of great importance. Numerous preventive strategies have been applied, with poor outcomes most of the time. This therapeutic shortcoming could be associated with the management strategies of AMI patients which include the quick transfer of the patient to the catheterization laboratory and the administration of contrast media. The use of contrast media is additionally per se nephrotoxic and furthermore the prompt response does not provide adequate time to implement the possible preventive measures. In that way, the conclusions regarding the true efficacy of these measures are less solid.

The goal of this review was to assess the incidence of AKI in AMI patients, how this incidence is affected by the diverse definitions, and if there is variability in the reported rates over recent years. Additionally, we sought to appraise the impact of AKI on short- and long-term prognosis of these patients. Finally, we reported on the current preventive measures as they are suggested in the current guidelines of various societies, we commented on the evidence that support them, and we reviewed the literature for other proposed therapeutic strategies, which either failed to prove their efficacy or they are not adequately confirmed yet.

Incidence of Acute Kidney Injury in Acute Myocardial Infarction Patients

The incidence of AKI in AMI patients as published in the medical literature fluctuates from 5.2 to 59%. This broad fluctuation is the result of the heterogeneity which characterizes the relevant clinical studies. The source of their heterogeneity stems not only from the AKI definition used but also from the clinical characteristics of the study population. A comprehensive presentation of the published studies which reported on AKI incidence in AMI patients is cited in Table 2 [10–75].

One of the largest studies was drawn from the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get With the Guidelines (GWTG), a nationwide sample of AMI patients admitted to 383 hospitals in the United States. The study enrolled 59,970 patients hospitalized with AMI [59]. The researchers used the AKIN criteria and they concluded that for the period from July 2008 to September 2009 the incidence of AKI was 16.1%. Using the same database, other researchers had similar results regarding AKI incidence (16.5%) for the time span between 2008 and 2012 including 76,500 AMI patients from 581 hospitals [33]. In the largest observational study including 147,007 elderly Medicare patients admitted for AMI from January 1994 through February 1996 as a part of the Cooperative Cardiovascular Project, an incident rate of AKI of 19.4% was reported [69].

The patients who undergo urgent coronary artery bypass grafting (CABG) constitute a particular category of AMI patients rather susceptible to AKI. In the HORIZONS-AMI and ACUITY trials, the patients who underwent percutaneous coronary intervention (PCI) had 16.1% frequency rate of AKI [40]. In contrast, in a study in which AMI patients were treated with CABG, the incident rate was nearly doubled (31.9%) [25]. Other possible predictors of AKI development in patients with AMI are hemodynamic instability and ejection fraction levels. When researchers assessed patients with

Table 2 Studies reporting incidence rates for acute kidney injury in patients with acute myocardial infarction

Author	Population (*n*)	Population characteristics	AKI incidence	AKI definition
Kuji et al. [10]	2798	AMI patients who underwent urgent coronary angiography	9.86%	Increase in serum creatinine ≥ 0.3 mg/dL or ≥ 50% within 48 h
Nakahashi et al. [11]	577	STEMI patients who underwent primary PCI	35.7%	Serum creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Tziakas et al. [12]	805	AMI patients	AKIN 7.2% RIFLE 6.7% AKIN + RIFLE 9.4%	AKIN, RIFLE and combination AKIN and RIFLE
Yuan et al. [13]	1061	AMI patients who underwent urgent coronary angiography	22.7%	Serum creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Katsuomi et al. [14]	806	AMI patients	18.1%	Serum creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Farhan et al. [15]	536	ACS patients who underwent coronary angiography	9.5%	RIFLE criteria
Shacham et al. [16]	842	STEMI patients with preserved EF who underwent primary PCI	6.1%	Increase in serum creatinine ≥ 0.3 mg/dL
Centola et al. [17]	402	STEMI patients who underwent primary PCI	17.4% with CIN criteria and 10.7% with AKIN criteria	Serum creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h and AKIN criteria
Valibey et al. [18]	2563	STEMI patients who underwent primary PCI	6.4%	Serum creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Neves et al. [19]	7808	ACS patients	17.5%	Increase in serum creatinine ≥ 0.3 mg/dL or ≥ 50%
Park et al. [20]	668	STEMI patients who underwent primary PCI	10.9%	Creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 48 h
Moriyama et al. [21]	760	AMI patients	13%	Increase in creatinine ≥ 0.3 mg/dL or ≥ 50% within any 48 h after admission
Kuboyama and Tokunaga [22]	247	STEMI patients who underwent primary PCI	27.1% according to the CIN definition 23.9% according to CI-AKI derived from RIFLE 15.8% according to CI-AKI derived from AKIN	Creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h or increase in serum creatinine ≥ 150% from baseline or a decrease in the eGFR ≥ 25% within 72 h or increase in serum creatinine ≥ 0.3 mg/dL or 150% from baseline within 72 h
Karamasis et al. [23]	454	STEMI patients who underwent primary PCI	14.1%	
Matezka et al. [24]	202	STEMI patients who underwent primary PCI	12.4%	Increase in creatinine ≥ 0.3 mg/dL or ≥ 50% within any 48 h after admission
Warren et al. [25]	1406	ACS patients treated with CABG	31.9%	Creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline
Marenzi et al. [26]	3771	STEMI patients who underwent primary PCI	15% (1) 14% (2) 7% (3)	(1) a relative serum creatinine increase ≥ 25% from hospital admission value (2) an absolute serum creatinine increase ≥ 0.3 mg/dL (3) an absolute serum creatinine increase ≥ 0.5 mg/dL
Tung et al. [27]	189	STEMI patients	19.6%	Increase in creatinine ≥ 0.3 mg/dL or ≥ 50% within any 48 h after admission
Kocas et al. [28]	600	NSTEMI patients who underwent PCI	15.4% if PCI < 24 h 14% if PCI 25–72 h 19.5% if PCI after 72 h	Creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Crimi et al. [29]	1443	ACS patients who underwent PCI	12.2%	Creatinine increase ≥ 25% from baseline
Vavalle et al. [30]	2578	STEMI patients who underwent primary PCI	18%	Decrease in eGFR > 25% from baseline

Table 2 (continued)

Author	Population (*n*)	Population characteristics	AKI incidence	AKI definition
Turan et al. [31]	312	NSTEMI patients who underwent early invasive procedure	9.6%	Creatinine increase ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Toso et al. [32]	615	Patients ≥ 75 years with NSTEMI	21%	Increase in creatinine ≥ 0.3 mg/dL or ≥ 50% within any 48 h after admission
Mody et al. [33]	76,500	Patients with AMI	16.5%	Increase in creatinine ≥ 0.3 mg/dL
Gaskina et al. [34]	216	STEMI patients who underwent primary PCI	20%	Increase in creatinine ≥ 0.3 mg/dL within any 48 h after admission or ≥ 50% within 7 days
Giakoppo et al. [35]	9512	AMI patients who underwent PCI	12.7%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Akin et al. [36]	630	STEMI patients who underwent primary PCI	12.5%	Increase in creatinine ≥ 0.3 mg/dL within 48 h
Watabe et al. [37]	1059	ACS patients who underwent emergent PCI	15.5%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 25% from baseline within 7 days
Kul et al. [38]	314	STEMI patients who underwent primary PCI	12.1%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Shackam et al. [39]	1248	STEMI patients who underwent primary PCI	9.2%	Increase in creatinine ≥ 0.3 mg/dL
Narula et al. [40]	3602	STEMI patients who underwent primary PCI	16.1%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 48 h
Kim et al. [41]	971	STEMI patients who underwent primary PCI	9.6%	Increase in creatinine ≥ 0.3 mg/dL within 24 h
Menzorov et al. [42]	146	STEMI patients subjected to thrombolytic therapy with streptokinase	51% with RIFLE 59% with AKIN	RIFLE and AKIN criteria
Liao et al. [43]	396	AMI patients	12.1%	Increase in creatinine ≥ 0.3 mg/dL within any 48 h after admission or ≥ 50% within 7 days
Liu et al. [44]	132	AMI patients who underwent PCI	9.8%	Increase in creatinine ≥ 0.3 mg/dL within any 48 h after admission
Liu et al. [45]	251	STEMI patients who underwent primary PCI	17.2% AKI (1) 8.8% AKI (2)	Increase in creatinine ≥ 0.3 mg/dL (1) or ≥ 0.5 mg/dL (2) or ≥ 50% within 48–72 h
Moriyama et al. [46]	760	AMI patients	13%	Increase in serum creatinine ≥ 0.3 mg/dL or ≥ 50% within any 48 h
Mizuno et al. [47]	102	STEMI patients who underwent primary PCI	10%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Hsieh et al. [48]	613	AMI patients who survived during hospitalization	12.8%	Increase in creatinine ≥ 50% or decrease in eGFR ≥ 25% within 7 days
Dos Santos et al. [49]	501	STEMI patients who underwent primary PCI	24.7%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 7 days
Choi et al. [50]	2110	AMI patients	11%	Increase in creatinine ≥ 0.3 mg/dL within any 48 h after admission or ≥ 50% within 7 days
Marenzi et al. [51]	3210	ACS patients	13%	Increase in serum creatinine ≥ 0.3 mg/dL or ≥ 50%
Kume et al. [52]	194	STEMI patients who underwent primary PCI	11.9%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 50% from baseline within the first 48 h
Rodrigues et al. [53]	1050	AMI patients	14.8% RIFLE criteria 36.6% KDIGO criteria	RIFLE or KDIGO criteria
Ando et al. [54]	481	STEMI patients who underwent primary PCI	5.2%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 72 h
Pyxaras et al. [55]	385	STEMI patients with preserved EF who underwent primary PCI	6.7%	Increase in creatinine > 25% or a decrease in the eGFR > 25% within 72 h
Lazaros et al. [56]	447	AMI patients	16.7%	Decrease in the eGFR > 25%
Lazzeri et al. [57]	681	STEMI patients with preserved EF who underwent primary PCI	12.9%	Increase in creatinine ≥ 0.3 mg/dL

Table 2 (continued)

Author	Population (*n*)	Population characteristics	AKI incidence	AKI definition
Queiroz et al. [58]	406	STEMI patients	20.4%	Increase in serum creatinine ≥ 0.3 mg/dL or ≥ 50%
Fox et al. [59]	59,970	AMI patients	16.1%	Increase in serum creatinine ≥ 0.3 mg/dL
Brueto et al. [60]	828	AMI patients	14.6%	Increase in creatinine ≥ 50% or decrease in eGFR ≥ 25% within 7 days
Hwang et al. [61]	2053	AMI patients	29.3%	Increase in serum creatinine ≥ 0.3 mg/dL or ≥ 50% within any 48 h
Lim et al. [62]	1146	AMI patients	19.3%	Increase in serum creatinine ≥ 0.3 mg/dL or ≥ 50% within any 48 h or oliguria ≤ 0.5 mL/kg/h for ≥ 6 h
Wi et al. [63]	1041	AMI patients who underwent PCI	14.2%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 25% from baseline within the first 48 h
Kim et al. [64]	855	STEMI patients	8.7%	Increase in creatinine ≥ 0.3 mg/dL
Amin et al. [65]	2098	AMI survivors	18.7%	Increase in creatinine ≥ 0.3 mg/dL
Senoo et al. [66]	338	Acs patients who underwent emergency PCI	28%	Increase in creatinine ≥ 25% from baseline within the first 72 h
Anzai et al. [67]	141	patients with reperfused first anterior STEMI who all underwent primary PCI	21.9%	Increase in creatinine ≥ 0.3 mg/dL from baseline within the first 48 h
Goldberg et al. [68]	1957	STEMI patients	15.1%	Increase in creatinine ≥ 0.3 mg/dL from baseline
Parikh et al. [69]	147,007	Patient ≥65 years with AMI	19.4%	Increase in creatinine ≥ 0.3 mg/dL from baseline
Passos et al. [70]	150	STEMI patients who underwent primary PCI	15.3%	Increase in creatinine ≥ 0.5 mg/dL or ≥ 25% from baseline
Bouzas-Mosquera et al. [71]	602	STEMI patients who underwent urgent PCI	12%	Increase in creatinine ≥ 0.5 mg/dL from baseline within the first 72 h
Latchamsetty et al. [72]	1417	ACS patients	8.82%	Increase in creatinine ≥ 0.5 mg/dL

Studies with patient population < 100 patients [73–75] are not reported in the table

ACS acute coronary syndrome, *AKI* acute kidney injury, *AKIN* Acute Kidney Injury Network, *AMI* acute myocardial infarction, *CIN* contrast-induced nephropathy, *EF* ejection fraction, *eGFR* estimated glomerular filtration rate, *KDIGO* Kidney Disease Improving Global Outcomes, *NSTEMI* non-ST elevation myocardial infarction, *PCI* percutaneous coronary intervention, *RIFLE* Risk, Injury, Failure, Loss, and End-Stage Kidney Disease, *STEMI* ST elevation myocardial infarction

cardiogenic shock, they reported that the incidence rate of AKI surged to 55% [75]. By comparison, in two other studies that reported AKI rates in AMI patients with preserved ejection fraction, the incidence rates were only 12.9% [57] and 6.2% [16].

An interesting debate is whether AKI incidence depends on the definition used. Two studies addressed this issue and assessed the same patients using different criteria (AKIN and RIFLE criteria) yielding contradictory results. The first concluded that AKIN criteria provide greater sensitivity than RIFLE criteria (AKI incidence 9.6 vs. 3.9% in favor of AKIN criteria); however, the second reported opposite results (23.9 vs. 15.8% in favor of RIFLE criteria) [22, 76]. Similarly, other researchers applied the KDIGO and RIFLE criteria on AMI patients showing that KDIGO surpass RIFLE criteria in AKI detection (36.6 vs. 14.8%) [53]. Finally, the comparison between AKIN criteria and Contrast-Induced Acute Kidney Injury (CI-AKI) criteria favored the second as more sensitive (10.7 vs. 17.4%) [17]. It is more than obvious that applying different definitions each time (using more strict or more liberal criteria) yields different incidence rates increasing or decreasing sensitivity and specificity each time.

Based on our review, we identified only one meta-analysis, which investigated the occurrence of AKI in AMI patients [77]. This analysis comprised 36 studies, with incidence ranging from 6.3 to 36.6% and a median value of 15.8%. Furthermore, it is worthy to cite two more papers, which investigated the fluctuation of AKI prevalence over time. The first one included 31,532 AMI patients hospitalized from 2000 to 2008 and reported that it steadily declined from 26.6% in 2000 to 19.7% in 2008 [78]. The decline was steeper among the patients treated with PCI (from 24.6 to 16.5%) in comparison with those treated conservatively (from 29.4 to 27%). The second one extracted data from a single center and reported a linear decline in the incidence of AKI (*P* value for trend 0.038) among 4307 ST elevation myocardial infarction patients from 2000 to 2015 [79].

Numerous studies have been published assessing possible predictors for AKI occurrence. Several risk scores have been developed in order to predict AKI; however, there are only a few that focused solely in patient with AMI. Among the most commonly cited risk factors for AKI are (a) reduced kidney function at presentation (defined as previous kidney disease, increased baseline creatinine levels, or decreased baseline glomerular filtration rate), (b) age, (c) hemodynamic instability (defined as the presence of shock, decreased systolic blood pressure, or use of intra-aortic balloon pump/inotropes), (d) heart failure (defined as previous history of heart failure, Killip class upon presentation, decreased ejection fraction, or increased left ventricular systolic ejection fraction), (e) coronary artery disease characteristics [defined as previous myocardial infarction, PCI, or CABG, presence of multi-vessel disease, anterior myocardial infarction, size of myocardial infarction, ST elevation or non-ST elevation myocardial infarction as an indication, catheterization that includes a PCI, emergency setting, thrombolysis in myocardial infarction (TIMI) flow post-PCI, or time to reperfusion], and (f) contrast volume used. Other predictors include various co-morbidities (anemia, diabetes mellitus, peripheral vascular disease, or hypertension) and possible nephrotoxic drugs (diuretics, metformin, or drugs that exert their action on renin-angiotensin-aldosterone axis, especially mineralocorticoid receptor antagonists) [80] (Fig. 1).

For the last two decades, interventional (PCI) rather medical treatment is the preferred strategy among patients presenting with AMI. Therefore, the use of contrast agents is warranted in the majority of AMI patients rendering these agents among the most commonly present and more easily modifiable risk factors for AKI occurrence, especially the type and the volume of the agent used. Contrast agents have been shown to cause the following detrimental changes within the glomerular and tubular apparatus: renal vasoconstriction, resulting in a rise in intrarenal resistance (decrease in renal blood flow and glomerular filtration rate and medullary hypoxia); epithelial vacuolization and dilatation and necrosis of proximal tubules; potentiation of angiotensin II effects, reducing nitric oxide and causing direct constriction of descending vasa recta, leading to formation of reactive oxygen species; increasing active sodium re-absorption in the thick ascending limbs of Henle's loop (increasing O_2 demand and consequently medullary hypoxia); direct cytotoxic effects on endothelial and tubular epithelial cells; and reducing cell survival, due to decreased activation of kinases involved in cell survival/proliferation [81].

According to our knowledge, there are no published studies assessing differences in the incidence of AKI in AMI patients depending on the type of infarction (ST elevation vs. non-ST elevation myocardial infarction). Review of the published observational AKI studies did not reveal significant differences on AKI incidence rate between ST elevation and non-ST elevation myocardial infarction. The only reported difference is the effect of time to reperfusion on AKI incident rates. Regarding occurrence of AKI, ST elevation myocardial infarction patients are more sensitive to time to reperfusion. However, there is a bulk of evidence suggesting that large either in size (as assessed by circulating levels of necrotic myocardial enzymes) or by location (anterior) myocardial infarctions are associated with an increased incidence of AKI and are considered as possible risk factors for future AKI [82].

Short-Term and Long-Term Prognosis

All studies investigating the toll that AKI might have on prognosis are suggesting a detrimental effect both for the short term and the long term in AMI patients. This detrimental effect was related neither with the follow-up period nor with AKI definition. As it was expected, it has been shown that AMI patients complicated with AKI have higher in-hospital mortality. Interestingly in these patients, this trend of increased mortality remains constant also out of hospital, even 3 years after their discharge [69]. The problem of heterogeneity among relevant studies still characterizes the assessment of AKI impact on prognosis. In Fig. 2 [10–75], these studies are summarized by reporting mean values for cumulative hazard ratios for mortality or major adverse cardiovascular events during hospitalization (7.9, 95% CI 2.5–13.2), up to 1 year since the index event (3.5, 95% confidence interval (CI) 2.7–4.3) and beyond 1 year (3.9, 95% CI 2.6–5.3).

As expected, in-hospital mortality is higher in patients who develop AKI with reported hazard ratios (HR) from 2 to over 30. Regarding long-term mortality, data cited suggest that it increases additively with longer follow-up periods as well as with increasing AKI severity. In a study of Fox et al., who utilized data from the ACTION Registry-GWTG, from 383 hospitals in the USA between July 2008 and September 2009, it was shown that in-hospital mortality was higher in patients with more advanced AKI (mild AKI: HR 2.4, 95% CI 2–2.7; moderate AKI: HR 4.5, 95% CI 3.9–5.1; severe AKI: HR 12.6, 95% CI 11.1–14.3) [59]. In the same study, there was a progressive increase in mortality rates, even in patients with minor increases in serum creatinine of 0.1 mg/dL, below the threshold of 0.3 mg/dL which is used in AKIN/KDIGO criteria [59]. Utilizing more recent data from (from 2008 to 2012), Mody et al. similarly reported that 1-year mortality increased in a dose-dependent manner across increasing severity of AKI [33]. Another study encompassed patients from two multicenter randomized trials (HORIZONS-AMI and ACUITY) showing a temporal increase in mortality rate for patients undergoing PCI from 4.9% at 30 days to 9.8% at 1 year [35]. A similar temporal trend in increasing mortality was shown also for patients undergoing CABG from 6.7% at 30 days to 10.4% at 1 year [25]. Other researchers assessed AMI patients 10 years after their initial hospitalization and reported not only

that mortality rates were proportionate to the corresponding AKI severity stage but also that this association continued to be significant even when death events occurring during the first 3 years were excluded from the analysis [69]. This finding may insinuate that the prognostic impact of AKI in AMI patients is not constraint only for the period of the acute event.

During recent years, an interesting notion has been postulated according which transient increases in creatinine (especially with that seen with diuretics or renin-angiotensin-aldosterone system medication use in heart failure patients) have no impact on patient prognosis. Several studies endeavored to elucidate this hypothesis. In the PREMIER study, only persistent AKI had statistically significant association with 4-year mortality compared to transient AKI (persistent AKI: HR 1.59, 95% CI 1.20–2.11 vs. transient AKI: HR 1.43, 95% CI 0.97–2.09) [65]. In contrast, other studies concluded that both transient and persistent AKI deteriorate patients' prognosis [50, 72]. To complicate things further, when researchers in another study divided AKI patients not only according to its duration but additionally according to its severity, only patients with transient mild AKI had similar prognosis compared to patients who did not developed AKI (HR for 3-year mortality 1.2, 95% CI 0.6–2.3, $P = 0.640$) [68]. Patients with moderate/severe but transient AKI were characterized by a poorer prognosis (HR for 3-year mortality 1.7, 95% CI 1.1–2.8, $P = 0.026$) [68].

Another interesting notion is whether the use of different AKI definitions has an effect in the accuracy of predicting AMI patients' prognosis. When RIFLE and KDIGO criteria were compared, the later criterion not only classified more patients as suffering from AKI but also characterized patients with worse prognosis [53]. This could be clinically translated as KDIGO criteria having greater sensitivity without losing their prognostic importance. Under the same notion, comparison between RIFLE and AKIN criteria showed that they both signal poor prognosis for AMI patients (RIFLE: HR for 5-year mortality 6.49, 95% CI 1.98–21.29, $P = 0.002$ vs. AKIN: HR 6.68, 95% CI 2.06–21.6, $P = 0.002$); however, AKIN criteria detected more AKI cases (9.6 vs. 3.9%) [76]. In contrast, another similar study showed that even though patients classified as suffering from AKI by AKIN criteria had worse prognosis than those detected by RIFLE, the latter classification yielded greater sensitivity [22]. Finally, another study comparing AKIN criteria with the CI-AKI definition showed that AKIN criteria had better correlation with 1-year mortality than the CI-AKI definition (AUC 0.798 vs. 0.775, $P = 0.033$) [17]. Fuelling the debate, a recent study suggested that a relative increase in serum creatinine of more than > 35% compared to admission baseline levels has the best correlation with the patients' mortality [29].

The only relevant meta-analysis showed that AKI-associated mortality in AMI patients is approximately threefold during the first 30 days (HR 3.1, 95% CI 2.6–3.6) and approximately twofold during the first year (HR 2.2, 95% CI 1.9–2.6) compared to patients who do not develop AKI [77]. Another interesting observation regarding the trend of AKI-related mortality in AMI patients is that the in-hospital mortality has declined steadily from 19.9% in 2000 to 13.8% in 2008 ($P = 0.003$) [78].

Preventive Strategies

The medical community in response to the frequent incidence of AKI in AMI patients and the detrimental impact on their prognosis applied numerous efforts in order to tackle this in-hospital complication. The main aim was to prevent the deterioration of kidney function and by those means to improve patients' prognosis. Many pathophysiological hypotheses have been raised and numerous clinical studies have been conducted in order to apply measures against these hypotheses, but they usually failed to state efficacy. Therefore, despite the multitudinous preventive strategies that have been examined during the last two decades, only a few of them have been embraced by the practicing physicians. The current guidelines issued by the European Society of Cardiology, KDIGO, and other societies contain the following recommendations for prevention of contrast-induced nephropathy (Table 3) [9, 83–89].

All societies agree that renal replacement therapy (RRT) should be reserved for patients when life-threatening changes in fluid, electrolyte, and acid-base balance exist [hyperkalemia, metabolic acidosis, symptoms or complications of uremia (for example, pericarditis or encephalopathy), fluid overload/pulmonary edema not responding to standard medical treatment]. The main guidance is to consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single urea and creatinine thresholds alone—when making the decision to start RRT.

According to all guidelines, the cornerstone for AKI prevention is optimal hydration. It has been suggested that optimal hydration achieves adequate intravascular volume and therefore adequate renal blood flow. Furthermore, the dilution of the nephrotoxic contrast agents and of the free radicals produced by the cellular necrosis attenuates their effect on kidney function [90]. Maioli et al. in a seminal paper showed that early hydration (before the procedure) of patients undergoing primary PCI reduced the incidence of AKI in comparison to patients with no or late hydration, albeit no effect on mortality or incidence of major clinical complications [90]. These results were corroborated by Jurado-Román et al., in a following study [91]. In the MYTHOS trial, the researchers investigated the effect of furosemide-forced diuresis and intravenous saline infusion matched with urine output on contrast-induced nephropathy (CIN) prevention in patients with chronic kidney disease (CKD) undergoing coronary procedures

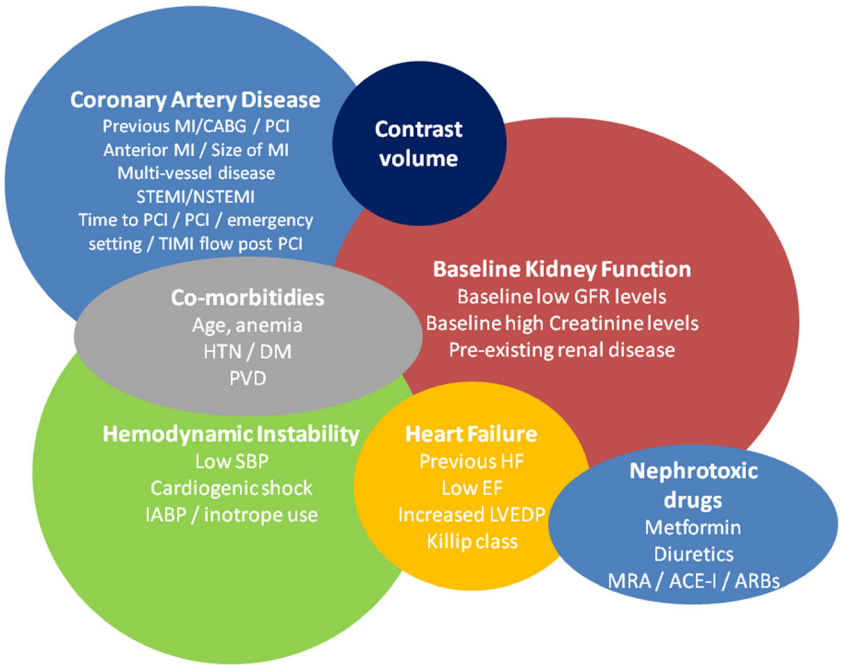

Fig. 1 Risk factors for AKI occurrence. AKI, acute kidney injury; CABG, coronary artery bypass grafting; DM, diabetes mellitus; EF, ejection fraction; GFR, glomerular filtration rate; HF, heart failure; HTN, hypertension; IABP, intra-aortic balloon pump; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SBP, systolic blood pressure; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction

[92]. The researchers concluded that furosemide-induced high urine output with matched hydration significantly reduces the risk of CIN [relative risk (RR) 0.16, 95% CI 0.04–0.58, $P = 0.003$) and may be associated with improved in-hospital outcome [92]. In a slight different approach but under the same notion in the POSEIDON clinical trial, researchers used the end-diastolic pressure of the left ventricle (LV) as an index for the optimal infusion rate [93]. Results from the aforementioned study showed that guiding hydration by means of LV end-diastolic pressure could prevent CI-AKI (RR 0.41, 95% CI 0.22–0.79, $P = 0.005$) [93].

The efficacy of sodium bicarbonate in the prevention of AKI in the setting of AMI is not consolidated, since studies investigating its ability to prevent AKI enrolled a limited number of AMI patients. In detail, there are four published meta-analyses that suggest that its utilization may be beneficial; however, they encompass only two to three studies in the setting of AMI [94, 95]. Regarding the use of *N*-acetylcysteine (NAC), although there was an initial enthusiasm based on favorable initial results [96], following randomized clinical trials failed to replicate its efficacy in preventing AKI. Recently, four different published clinical trials reported that the use of NAC has no significant impact on AKI incidence [97–100]. In contrast, there are more robust data regarding the use of statins in prevention of AKI. The hypothesis underlying the use of statins in such a clinical setting is that their pleiotropic and anti-inflammatory actions of these drugs are responsible for the protection they provide to kidney function [101]. Three meta-analyses have been published recently which assessed the use of statins regarding their AKI prevention efficacy in the setting of AMI [102–104]. All three meta-analyses reported an AKI cumulative relative risk reduction between 50 and 60% with pretreatment with statins (OR 0.37, 95% CI 0.26–0.53 [102]; OR 0.39, 95% CI 0.25–0.61 [103]; and OR 0.48, 95% CI 0.35–0.66 [104]).

All societies agree that the volume and the composition of the contrast agent used during coronary angiography/intervention are very important regarding the incidence of kidney injury. Although initially it was the absolute amount of these agents which was thought to be responsible for inflicting kidney injury, later published evidence suggested that more significant was the ratio of absolute volume used to estimated GFR [105–108]. Multiple moderate-sized studies have initially supported the use of a threshold of a 5× body weight/serum creatinine as the safe upper limit for contrast, which is known as the maximal acceptable contrast dose (MACD) [109, 110]. However, contrast-induced injury has been anecdotally demonstrated at lower doses of contrast, and the need for better dosing strategy has been recognized for a long time. Therefore, the application of the ratio of the contrast volume used to estimate GFR was deemed more precise and practical. Three different approaches have been published regarding the cut-off of this ratio. Initially, it was recommended not to be bigger than 3.7 [105], a slightly different proposal defined the threshold at 3.6 [106], whereas other researchers proposed the ratio not to transcend above 2 [107]. In a similar way, recently it was suggested that the ratio of volume of contrast agent used to calculated creatinine clearance could yield accurate prediction for possible AKI and the threshold of this ratio should not exceed 3 [108]. This study showed that the association between the risk of AKI and the volume to GFR ratio is continuous and unfortunately AKI incidence is probable even in cut-offs < 2 especially in high-risk sub-populations [108]. Therefore, the authors

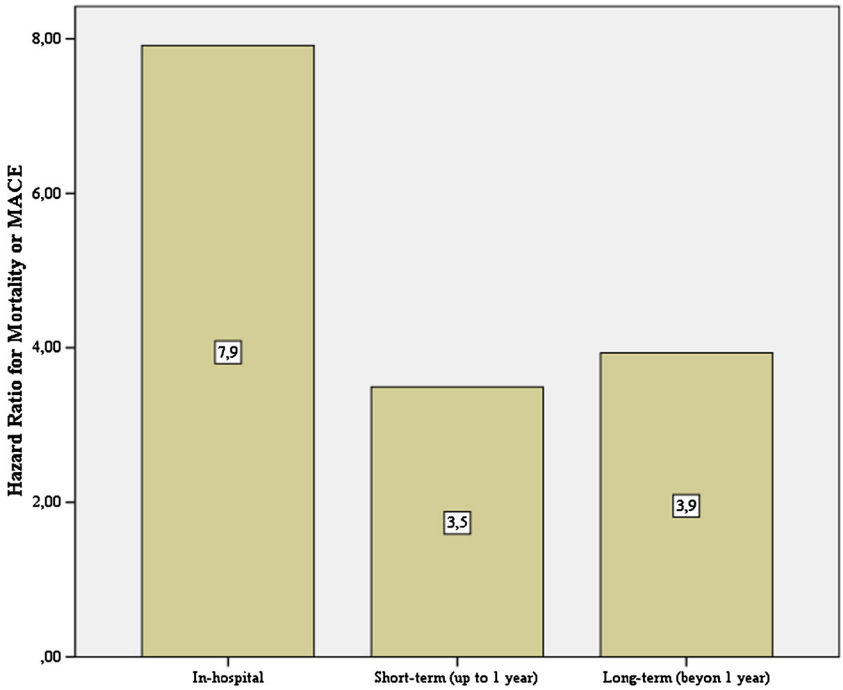

Fig. 2 Short-term and long-term prognosis of AMI patients complicated with AKI. Bars represent mean values for cumulative hazard ratios for mortality or MACE during hospitalization, up to 1-year follow-up since the index event and longer than 1 year using different criteria for AKI (AKIN, RIFFLE, CIN-AKI, and arbitrary criteria). For in-hospital prognosis, the following studies were used: [10, 15, 21, 26, 31, 32, 38, 43, 46, 49, 59, 61, 62, 64, 66, 71–73, 75]. For short-term prognosis, the following studies were used: [25, 28, 32–35, 41, 53, 55, 56, 60, 70]. For long-term prognosis, the following studies were used: [11, 15–17, 20, 22, 29, 31, 37, 40, 48, 50, 52, 65, 67–69, 71]. AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; AMI, acute myocardial infarction; CIN, contrast-induced nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; MACE, major adverse cardiovascular events; RIFLE, Risk, Injury, Failure, Loss and End-stage kidney disease

recommended the use of as low as possible of contrast volume during PCI [108]. However, as AKI is a multifactorial complication, a preventive strategy should not focus on a single dimension such as the contrast volume used. Different predisposing aspects of this complex complication should be dealt with in a multi-dimensional strategy for these measures to be effective.

Additionally, the composition of the contrast agent is of major importance as far as it concerns its possible effect on kidney function. It has been shown that the use of high-osmolar agents has detrimental effects on kidney function and therefore they are not recommended. Furthermore, iso- and low-osmolar agents have been shown to be safer regarding AKI and also the comparison between iso-osmolar and low-osmolar agents failed to favor any of the two [111, 112]. Based upon these published data, latest guidelines recommend the use of either iso- or low-osmolar contrast agents.

During recent years, there was a significant shift in the practice of coronary angiography and or interventions, as nowadays the majority of interventional cardiologists prefer the radial access which proved to reduce mortality and periprocedural complications especially in the setting of an ACS [113]. A hypothesis has been raised according which the observed less bleeding events associated with radial access could have an impact on preserving kidney function as it well known that anemia may predispose to AKI [114]. This hypothesis has been corroborated in two meta-analyses that showed a cumulative relative risk reduction of 50–60% for AKI with the use of radial access in the clinical setting of AMI (OR 0.42, 95% CI 0.24–0.72 [115] and OR 0.49, 95% CI 0.32–0.75 [116]). Occurrence of bleeding complications after PCI has been associated with post-PCI AKI [117]. As transradial approach is associated with less bleeding complications compared to transfemoral approach, probably the reduction in bleeding rates is the link between radial access and its renal protective effects [117]. The speculated causative effect of bleeding may be related to the occurrence of AKI via the associated hypotension and subsequent renal hypoperfusion observed with larger bleeds [117]. Beyond hemorrhagic complications, microembolization has been observed in patients undergoing PCI and its role has been implicated in post-PCI AKI. PCI performed using transfemoral approach involves the transit of wires and catheters through a significantly long segment of the aorta, increasing the probability of atheroembolic renal injury leading to AKI. The reno-protective effect of radial access might be related to fewer atheroemboli in view of the lack of need to navigate through descending thoracic and abdominal aorta [117].

An interesting debate regarding AKI incidence in the clinical setting of AMI is whether the timing of coronary reperfusion

Table 3 Recommendations for prevention of contrast-induced nephropathy

Recommendation	Dose	Class/level
European Society of Cardiology		
Patients undergoing coronary angiography		
Patients should be assessed for risk of CI-AKI		IIa/C
Patients with moderate-to-severe CKD		
Hydration with isotonic saline is recommended		I/A
Use of low-osmolar or iso-osmolar contrast media is recommended	< 350 mL or < 4 mL/kg or total contrast volume/GFR < 3.4	I/A
Short-term, high-dose statin therapy should be considered	Rosuvastatin 40/20 mg or atorvastatin 80 mg or simvastatin 80 mg	IIa/A
Iso-osmolar contrast media should be considered over low-osmolar contrast media		IIa/A
Volume of contrast media should be minimized		IIa/B
Furosemide with matched hydration may be considered over standard hydration in patients at very high risk for CIN or in cases where prophylactic hydration before the procedure cannot be accomplished	Initial 250 mL IV bolus of NS over 30 min (reduced to 150 mL in case of LV dysfunction) followed by an IV bolus (0.25–0.5 mg/kg) of furosemide. Hydration infusion rate has to be adjusted to replace the patient's urine output. When the rate of urine output is > 300 mL/h, patients undergo the coronary procedure. Matched fluid replacement maintained during the procedure and for 4 h post-treatment	IIb/A
NAC administration instead of standard hydration is not indicated		III/A
Infusion of sodium BIC 0.84% instead of standard hydration is not indicated		III/A
Severe CKD		
Prophylactic hemofiltration 6 h before complex PCI may be considered	Fluid replacement rate 1000 mL/h without negative loss and NS hydration continued for 24 h after the procedure	IIb /B
Prophylactic renal replacement therapy is not recommended as a preventive measure		III/B
American College of Cardiology/American Heart Association		
Minimization of contrast volume		
Optimal hydration		
Kidney Disease: Improving Global Outcomes		
We suggest using protocol-based management of hemodynamic and oxygenation parameters to prevent development or worsening of AKI in high-risk patients in the perioperative setting or in patients with septic shock		2C
In critically ill patients, we suggest insulin therapy targeting plasma glucose 110–149 mg/dL		2C
We suggest achieving a total energy intake of 20–30 kcal/kg/d in patients with any stage of AKI		2C
We suggest to avoid restriction of protein intake with the aim of preventing or delaying initiation of RRT	We suggest administering 0.8–1.0 g/kg/day of protein in non-catabolic AKI patients without need for dialysis, 1.0–1.5 g/kg/day in patients with AKI on RRT (2D), and up to a maximum of 1.7 g/kg/day in patients on continuous renal replacement therapy (CRRT) and in hypercatabolic patients	2D
We recommend not using diuretics to prevent AKI		1B
We suggest not using diuretics to treat AKI, except in the management of volume overload		2C
We recommend not using low-dose dopamine to prevent or treat AKI		1A
We suggest not using fenoldopam to prevent or treat AKI		2C
We suggest not using atrial natriuretic peptide to prevent or treat AKI		2C/2B
We suggest not using aminoglycosides for the treatment of infections unless no suitable, less nephrotoxic, therapeutic alternatives are available		2A

Table 3 (continued)

Recommendation	Dose	Class/level
We suggest that off-pump coronary artery bypass graft surgery not be selected solely for the purpose of reducing perioperative AKI or need for RRT		2C
We recommend not using oral or IV NAC for prevention of postsurgical AKI		1A
National Institute for Health and Care Excellence		
Ensure that systems are in place to recognize and respond to oliguria (urine output less than 0.5 mL/kg/h)		
Offer intravenous volume expansion to adults having iodinated contrast agents	Offer either isotonic sodium BIC or 0.9% NS	
Consider temporarily stopping ACE inhibitors and ARBs in adults having iodinated contrast agents if they have chronic kidney disease with an GFR less than 40 mL/min/1.73 m^2		
Do not routinely offer loop diuretics to treat acute kidney injury. Consider loop diuretics for treating fluid overload or edema		
Do not offer low-dose dopamine to treat acute kidney injury		
Society of Coronary Angiography and Interventions		
Withhold, if clinically appropriate, potentially nephrotoxic drugs including aminoglycoside antibiotics, anti-rejection medications and NSAID		
Administer NAC (equivocal data)	600 mg administered orally q 12 h 4 doses beginning prior to contrast	
Administer hydration	Administer a total of at least 1 L of NS beginning at least 3 h before and continuing at least 6–8 h after the procedure. Initial infusion rate 100–150 mL/h adjusted post-procedure as clinically indicated	
Administer Sodium BIC (limited data)	154 mEq/L at 3 mL/kg/h starting 1 h before contrast. 154 mEq/L at 1 ml/kg/h for 6 h following contrast	
Regarding radiographic contrast media: minimize volume and use low- or iso-osmolar contrast agents (on going data)		

Italics represent distinct categories of patients requiring specific preventive actions

ACE angiotensin-converting enzyme, *AKI* acute kidney injury, *ARBs* angiotensin receptor blockers, *BIC* bicarbonate, *CIN* contrast-induced nephropathy, *CKD* chronic kidney disease, *GFR* glomerular filtration rate, *IV* intravenous, *LV* left ventricular, *NAC N*-acetylcysteine, *NS* normal saline, *NSAIDs* non-steroid anti-inflammatory drugs, *PCI* percutaneous coronary intervention, *RRT* renal replacement therapy

could have an impact. It is logical to hypothesize that in patients with risk factors for AKI, a prudent approach would be to delay coronary reperfusion and the associated use of "nephrotoxic" contrast agents. However, data from published studies are contradictory. In one study, which enrolled ST elevation myocardial infarction patients, the incidence of AKI was increased in parallel with the delay of revascularization [118]. In another study enrolling non-ST elevation myocardial infarction patients, time to reperfusion had no prognostic value [28]. This data probably underline the hypothesis that AKI incidence in AMI patients is not only dependant on the known nephrotoxic effects of contrast agents but also on other factors such as hemodynamic stability, adequate kidney perfusion, baseline kidney function, hemoglobin levels, atherosclerosis of other vascular beds, and others. Timely coronary reperfusion may have a beneficial effect on most of these aforementioned factors.

Another novel approach regarding prevention of AKI in AMI patients was the application of remote ischemic conditioning [119]. Remote ischemic conditioning, including remote ischemic pre-conditioning and remote ischemic post-conditioning, is a method that applies brief non-lethal episodes of ischemia and reperfusion to an organ or tissue (heart/vasculature) that is remote from the target organ or tissue (kidney) [119]. The associated nephroprotective actions of this novel method were attributed to the increased nitric oxide (NO) production and the reduction of free oxygen radicals [119]. One recent meta-analysis showed the effectiveness of these methods to prevent AKI in patients undergoing elective coronary angiography but failed to demonstrate similar results in ACS patients, possibly due to the limited number of incorporated studies and the small study populations enrolled [120].

Withholding metformin has been suggested by some guidelines as a means to prevent the development of AKI.

However, randomized clinical data do not show that chronic metformin treatment prior to primary PCI had a significant impact on CI-AKI [121, 122]. Finally, published data regarding the use of natriuretic peptides [123] and magnesium [124] as preventive measures for AKI were promising; however, the under-investigation study populations were rather small to draw definitive conclusions. Larger clinical studies are required in order to extrapolate these results to all AMI patients.

A very recent survey from the Society of Cardiovascular Angiography and Interventions (SCAI) investigated the contemporary practice patterns related to the risk of AKI in the catheterization laboratory. The majority of cardiologists participating in this survey reported practice patterns consistent with guideline and evidence-based recommendations. However, over 40% of responses to questions were inconsistent with these recommendations, suggesting continued opportunities for education and quality improvement concerning AKI prevention [125].

Discussion

AKI is a common complication in the setting of AMI, with detrimental effects on patients' prognosis, not only during hospitalization but also for the long-term. According to our point of view, the rather disproportionate reference of AKI in current AMI guidelines may contribute to inadequate vigilance, under-diagnosis, and ineffective management. Additionally, under the same notion, many physicians might underestimate creatinine changes during hospitalization and falsely attribute them to laboratory measurement variability.

Physicians should not approach in-hospital changes in creatinine values as a product of laboratory or biologic variation or transient, not being associated with prognosis but rather as an adverse event which requires a more active and preemptive course of actions. Modern laboratory measurements minimize the effects of analytic variations, and furthermore, several studies suggest that a creatinine increase even below the threshold for AKI definition (0.3 mg/dL) may be associated with augmented mortality.

A common limitation of the majority of studies that assess the incidence and impact of AKI in the AMI patient population is to exclude patients with end-stage renal disease, patients who are very old-aged, and finally patients with cardiogenic shock. The aforementioned selection bias renders study populations to include more "healthy" AMI patients and therefore probably lead to an underestimation of the true AKI incidence and impact on prognosis. Moreover, this limitation hinders the assessment of proposed preventive strategies on patients who are more vulnerable that is patients with a history of chronic kidney disease, the very elderly, and those patients with hemodynamic instability.

An unresolved issue is the association between AKI and mortality. The remaining question is whether AKI could lead to mortality per se via distinct pathophysiologic pathways or mortality just a result of frailty? It is known that ischemic injury deteriorates kidney function progressively in time and also predisposes to hypertension [126, 127]. Additionally, kidney dysfunction is characterized by an inflammatory, pro-oxidative, and pro-thrombotic state [65]. In summary, AKI is associated with a high mortality that may be due to traditional and non-traditional complications. Traditional complications include well-recognized renal adverse events such as hyperkalemia, acidosis, and volume overload that could lead to increased mortality and morbidity through arrhythmogenicity and decompensation of heart failure. Non-traditional complications include an augmented inflammatory, oxidative, and apoptotic environment that could lead to a propensity for either thrombosis or bleeding. Platelet defects range from diminished responsiveness to platelet agonists like ADP, abnormal platelet adherence to foreign surfaces, reduced platelet pro-coagulant activity, decreased thromboxane and cyclic AMP (cAMP) production, decreased platelet membrane glycoprotein Ib (GPIb) expression, or in the other hand increased platelet turnover and overexpression of the thrombin receptor protease-activated receptor-1 (PAR-1) [128]. Moreover, in patients with compromised renal function, there is evidence of endothelial dysfunction characterized by an abnormal prostacyclin and thromboxane production and more importantly by an increased production and abnormal activity of von Willebrand factor [128]. Therefore, the possible association between AKI and increased mortality in patients with kidney failure may lie under two opposite hemostatic complications: a bleeding diathesis and a thrombotic predisposition [128]. Finally, the presence of reduced glomerular filtration rate could prohibit the use of treatment modalities that could otherwise be beneficial such as medication that have an effect on renin-angiotensin-aldosterone axis. More extensive research is required in this direction, in order to better understand the pathophysiologic consequences of AKI and their association with mortality.

Although there is a bulk of published evidence suggesting the importance of AKI, we must underscore that a great number of studies, especially in the setting of contrast-induced nephropathy, question not only the impact of AKI on prognosis but also whether AKI is a true "disease" state [129]. An argument against this hypothesis is that the pathophysiology of kidney injury after a myocardial infarction is far more complex than CI-AKI, and according to our point of view, it would not be appropriate to confound these two distinctly different kidney injuries, although some times the latter may add up to the former as in the setting of invasive management of myocardial infarction patients.

Under the same notion, regarding prediction of AKI the bulk of published evidence derive from studies investigating the predictive ability of risk scores for CI-AKI in mixed

populations including stable and unstable (acute coronary syndromes) coronary artery disease patients after PCI in a variety of clinical settings [elective, emergent (< 24 h) or urgent (≥ 24 h) basis]. On the other hand, there is scarcity of available data regarding predictive risk scores for AKI in patients after a myocardial infarction irrespective of the use of contrast agents. Zambetti et al. published recently the UT-AKI index, a risk score incorporating variables such as the use of intra-aortic balloon pump, hypotension, ejection fraction, age, chronic kidney disease, left ventricular end-diastolic pressure, and estimated GFR with modest predictive ability [area under the curve (AUC) 0.760] [130]. Kul et al. published the predictive ability of Zwolle risk score (Killip class, TIMI flow, age, three-vessel disease, anterior myocardial infarction, and ischemic time) in AMI patients with good predictive ability (AUC 0.850) [38]. Liu et al. assessed the prognostics characteristics of the GRACE risk score for CI-AKI (age, Killip class, systolic blood pressure, heart rate, creatinine levels, myocardial necrosis enzyme levels, and presence of ST deviation on ECG) yielding moderate results also (AUC 0.668 to 0.788) [45]. Although Mehran's risk score had not been derived and validated solely in AMI patients population, its application in patients presenting with AMI is characterized with a moderate predictive value (AUC 0.790 [130]; AUC 0.780 [131]). Very recently, a new risk score was developed for prediction of AKI in AMI patients incorporating variables such as cardiac arrest, decompensated heart failure on presentation, diabetes mellitus, hypertension, anemia, impaired renal function, and tachycardia on presentation with repeatedly moderate prognostic ability (AUC 0.760) [132]. Taken altogether, the practical utility of the above risk scores in prediction of AKI among AMI patients is limited since the clinical application of these tools is characterized with moderate sensitivity and specificity (approximately 70–80% for both) rendering false-negative and false-positive prediction rates high.

Finally, it has been shown that AKI incidence has declined considerably during the last decade [78]. Of note, this declined occurred in the absence of a great array of preventive measures or of a significant shift in practice. So far, only volume loading for the prevention of contrast-induced AKI and avoidance of drugs that might contribute to AKI have proven to be of value, whereas results for other strategies are inconclusive (sodium bicarbonate, *N*-acetylcystein, ascorbic acid, theofyllin, statins and others) or indicate potential harm [132–134]. The majority of published data assessing the effects of preventive measures showed weak data regarding their ability to lower AKI incidence risk [135, 136]. Moreover, data regarding the ability of these preventive measures to lower cardiovascular mortality are either scarce are of low quality [135, 136]. Although occurrence of AKI is associated with increased mortality and morbidity, the association between lowering AKI incidence by preventive measures and the improvement on long-term cardiovascular prognosis is further complicated by the fact that the long-term prognosis after AKI varies depending on cause and clinical setting, but it may also, mostly, be explained by underlying post-AKI renal function and existing co-morbidities rather than the AKI episode itself [137]. With regards to the long-term effects, the consideration that outcome is a simple binary endpoint of dialysis or not, or survival or not, is overly simplistic, with the reality being much more complex [138]. All of the above underscore the need for larger and longer term studies focusing not just on short-term AKI but also long-term adverse cardiovascular events. To make matters worse, the cornerstone of the proposed preventive strategies, hydration, is under question, as a recent study failed to prove its usefulness in patients referred for an elective procedure requiring the administration of intravascular iodinated contrast material [139]. Moreover, the rate of hydration used is also debatable in the clinical setting of an AMI complicated with AKI as acute reductions in the systolic performance of the left ventricle in the presence of oliguria may lead to volume overload and congestion [135].

Are the preventive measures that already have been used so efficient or is something there concerning kidney protection eluding from us? Are differences in AKI definitions and in AKI reporting obscuring the picture or the large variation in AKI incidence among different hospitals and departments conceals truly preventive practices? Further studies are also needed in this direction.

An interesting clinical scenario has been identified in the clinical setting of an acute ST elevation MI. As according to current guidelines, the majority of these patients should be addressed invasively as soon as possible to first medical contact, the question prevailing is which reno-protective measures should be applied even before kidney function is known? The answer is far more straightforward; however, use of the lowest possible volume of low- or iso-osmolar contrast agent, adoption of staged procedures in patients with high complex coronary artery disease anatomy, avoidance of nephrotoxic drugs, and maintenance of adequate kidney perfusion are logical preventive measures to follow. Furthermore, prophylactic use of intravenous volume expansion with isotonic saline or sodium bicarbonate prior to the procedure and continuing for 6 h post-procedure is an additional alternative although systolic performance of the left ventricle should be taken into account.

Conclusions

AKI is one of the more common complications in the setting of AMI with significant detrimental impact on patients' prognosis. Despite the limited number of practices and measures to prevent it, there is a steady decline in its incidence during the last years. However, further research is warranted in order to

illuminate many "gray" areas regarding AKI pathophysiology, diagnosis, treatment, and prevention in the setting of AMI.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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