



Sodium Bicarbonate versus Statins to Prevent Contrast-induced Acute Kidney Injury: A Comprehensive Review

Sanam Dolati^{1,2}, Ata Mahmoodpoor³, Nafiseh Gharizadeh², Saina Gholipouri⁴, Hassan Soleimanpour⁵

¹Physical Medicine and Rehabilitation Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

²Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.

³Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

⁴Department of Medical Sciences, University of Western Ontario, Ontario, Canada.

⁵Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran.

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Abstract

Iodinated contrast agents are commonly used in diagnostic radiography techniques along with therapeutic interventions. Contrast-Induced Acute Kidney Injury (CI-AKI) is a significant problem of all angiographic procedures, triggered by the use of Iodinated Contrast Media (ICM). There are conflicting data concerning the prevention and treatment of CI-AKI. Numerous approaches have been studied to prevent CI-AKI, but the therapy of choice remains undetermined. The cornerstones of CI-AKI prevention include low-osmolar ICM and intravenous hydration. The recommended hydration must be achieved by means of an isotonic solution of saline. Statins were tested against AKI due to their anti-inflammatory action and antioxidant effect on endothelial function. Novel approaches are required to investigate the short-term effects of high dosage atorvastatin versus sodium bicarbonate on CI-AKI prevention. The objective of this review is to compare the findings of various studies that had applied different doses of statins, sodium bicarbonate, and other agents for preventing CI-AKI.

Introduction

Contrast-Induced Acute Kidney Injury (CI-AKI) is the third important cause of hospital-acquired AKI, a frequent problem after contrast angiography accompanied by the high risk of increasing short- and long-term mortality rates.¹ CI-AKI accounts for about 11% of renal failure cases.² Administration of contrast agents stimulates rapid renal vasodilatation followed by persistent vasoconstriction that causes medullary ischemic hypoxia, which is a serious factor in the pathogenesis of CI-AKI; besides, it stimulates free oxygen radicals, apoptosis of renal tubular cells, and a higher Serum Creatinine (SCr) level.³ CI-AKI can be defined as the relative increase rate of > 25% or absolute increase of 0.5 mg/dL and \geq 0.3 mg from baseline serum creatinine measurement within 48–72 hours of contrast exposure.^{4,5} The mechanism of contrast-induced AKI is complex, remains completely vague, and probably multifactorial.⁶

Patients with renal impairment at baseline, acute coronary syndrome, and those experiencing Percutaneous Coronary Intervention (PCI) run the risk of contracting CI-AKI.⁷ CI-AKI occurs commonly in patients predisposed to risk factors such as Chronic Kidney Disease (CKD) and several comorbidities (chronic heart failure, anemia, and hypo-albuminemia).⁸ Among the mentioned risk factors,

CKD is the most important and common risk factor in contracting CI-AKI.⁹

Nowadays, there is no definitive treatment for CI-AKI, which is the reason why a noticeable number of particular interventions for preventing CA-AKI have been studied.¹⁰ Preventive strategies for CI-AKI include hydration with normal saline (NLS), sodium bicarbonate (NaHCO_3), hydration with statins, N-acetylcysteine (NAC), atrial natriuretic peptide, ascorbic acid, and nifedipine, prophylactic hemofiltration, and hemodialysis. These strategies can reduce contrast media volume and avoid the necessity of taking nephrotoxic drugs.^{11,12} Before and after contrast agent administration, hydration is considered as the main preventive approach that be accompanied by such side effects as the risk of pulmonary edema in patients with attenuated cardiac and kidney functions.¹³

Reports on the efficiency of statins in the prevention of CI-AKI remain controversial. Sodium bicarbonate has exhibited no beneficial role in preventing CI-AKI, reducing major adverse renal and cardiovascular events, and improving survival from dialysis after 5 years.¹⁴ Some of the studies that have investigated the role of different mentioned agents in preventing CA-AKI are reviewed below.

*Corresponding Author: Hassan Soleimanpour, E-mail: h.soleimanpour@gmail.com

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Sodium Bicarbonate

Sodium bicarbonate (9 ml/Kg (Intravenous (iv))) is used in decreasing CI-AKI development risk by expanding plasma volume, reducing the acidification of urine and renal medulla (pH raising), preventing ROS development, and scavenging peroxynitrite and other reactive species generated from nitric oxide, thus reducing the cases of renal injuries caused by free radicals compared to hydration with hypotonic saline solution alone or with N-acetyl cysteine (iv).^{15,16} Several studies have reported the efficiency of sodium bicarbonate in CI-AKI prevention.

In a randomized clinical trial performed by Pakfetrat *et al.*¹⁷ it was found that in the case of patients undergoing coronary angiography or PCI, both sodium bicarbonate and oral acetazolamide (AZ) decreased the risk of CI-AKI to a greater degree than normal saline. Hypokalemia was shown to occur following the infusion of sodium bicarbonate and normal saline, which could lead to severe life-threatening ventricular arrhythmia; therefore, close monitoring of serum potassium (K⁺) is required during bicarbonate and normal saline infusion.¹⁷

Masuda *et al.*¹⁸ revealed that sodium bicarbonate infusion was more efficient than sodium chloride in the prevention of CIN in patients experiencing an emergency coronary procedure, but N-acetylcysteine did not reduce the probability of CIN incidence.^{19,20}

A randomized single-center trial was conducted on 111 patients with acute coronary syndrome undertaking emergency PCI (the RENO study) by Recio-Mayoral.²¹ The results demonstrated that rapid intravenous hydration with sodium bicarbonate plus N-acetylcysteine before contrast injection prevented contrast-induced kidney injury (1.8% cases of incidence) more efficiently than after the procedure (21.8% cases of incidence).²¹ A prospective, randomized trial (REINFORCE) by Adolph *et al.*²² pointed to the homogeneously low rate of contrast-induced nephropathy after exposure to nonionic, iso-osmolar iodixanol in spite of hydration with sodium bicarbonate or sodium chloride solution. Brar *et al.*²³ conducted a randomized controlled study with a population of 353 patients undergoing coronary angiography. According to the results, hydration with sodium bicarbonate did not outperform sodium chloride in patients with moderate to severe CKD.²³ A large retrospective analysis of patients at the Mayo Clinic Rochester found a link between the higher probability of CI-AKI occurrence and the administration of sodium bicarbonate.²⁴

A symptomatic review and meta-analysis of 192 identified publications including 18 studies and 3055 patients was performed by Hoste *et al.*²⁵ The results of the prospective trials confirmed the protective effects of sodium bicarbonate on the risk of CI-AKI without impact on mortality.

The Remedial II study was a randomized trial that compared the development of renal damage with Renal Guard System in control group (infusion of sodium bicarbonate and N-acetylcysteine) with patients suffering

from the elevated risk of contrast media nephropathy.²⁶ It has been proven that RenalGuard therapy is able to attenuate the development of contrast nephropathy by 3 times and reduce the corresponding mortality rates, need for dialysis, stroke onset, and post PCI coronary syndromes.²⁶ RenalGuard therapy functions better than conventional hydration regimens in prevention of CIN in high-risk patients.²⁷ The results of one multicenter clinical trial showed that hydration with sodium bicarbonate employed to prevent CIN did not outperform saline in treating patients exposed of risk of experiencing cardiac catheterization.²⁸

Results of a multicenter, randomized, controlled trial performed by Klima *et al.*²⁹ showed that volume supplementation with 24 h sodium chloride in the prevention of CIN was more efficient than 7 h sodium bicarbonate.²⁹

Boucek *et al.*³⁰ conducted a randomized double-blind research that included a sodium chloride hydration-controlled study of sodium bicarbonate in 120 diabetic patients using low-osmolar contrast media. As a result, sodium bicarbonate did not confer protection against CIN more than sodium chloride-based hydration and no substantial differences were seen between Scr and eGFR and, also, between the oxidative stress parameters. One single-center, randomized clinical trial including 107 patients was directed at Emergency Department (ED) and it was found that none of the short-term protocols with normal saline, N-acetylcysteine, or sodium bicarbonate was efficient in treating ED patients needing Contrast Enhanced Computed Tomography (CECT) who had a moderate or high risk of CIN.³¹ Intravenous normal saline and intravenous sodium bicarbonate solutions provide efficient prophylaxis. Bicarbonate has not been favored over saline in studies that have already assessed hydration protocols in patients having CECT.³²

Results of multicenter randomized trials showed that 1-hour bicarbonate hydration was not inferior to saline in CKD patients undergoing intra-arterial contrast processes, but it could only shorten the hospitalization length.³³ Results of another multicenter, open-label, randomized, controlled trial conducted on patients with moderate renal impairment undergoing cardiac catheterization and percutaneous coronary intervention (CONTRAST) showed that a combination of sodium bicarbonate regime and oral N-acetylcysteine did not function better than individual regimens and, therefore, 12-hour sustained sodium chloride pre-hydration regimen was more protective than the 1-hour shortened sodium bicarbonate regimen.³⁴

The PRESERVE study comprised those patients with a high risk of renal failure after contrast administration and revealed that periprocedural intravenous sodium bicarbonate did not have an advantage over intravenous sodium chloride in terms of preventing death, inhibiting CA-AKI, or need for dialysis.³⁵ Moreover, hydration with sodium bicarbonate or N-acetylcysteine is not

recommended for long-term use in high-risk patients receiving angiography.³⁶

The results of a prospective, single-center trial including 300 patients who were scheduled for angiography demonstrated that sodium bicarbonate had greater protective effect than N-acetylcysteine or Ringer's Lactate (RL) on CIN prevention.³⁷ However, recently, the AMACING trial which compared hydration with the case if no hydration recommended that keeping patients hydrated with eGFR > 29 mL/min/1.73 m² might be a safer strategy in patients receiving CM.³⁸

Recently, Cai *et al.*³⁹ conducted a systematic review and Bayesian network meta-analysis and found that RenalGuard system was the best, followed by hemodynamic guided hydration, in dealing with patients with CI-AKI.

In conclusion, the role of sodium bicarbonate in CI-AKI prevention needs to be clarified and further studied.

Statins

Statins are lipid-lowering drugs that play an anti-inflammatory and detoxifying role in CI-AKI prevention.⁴⁰ Periprocedural statins exhibit positive effect on nephroprotection and their antioxidant and anti-inflammatory effects can reduce the CI-AKI rate by 58%.⁴¹ Furthermore, statins may reduce the reabsorption of contrast agents in renal tubules, thus decreasing toxicity within them.⁴² European Society of Cardiology (ESC) guidelines (2018) recommend considering a pre-treatment with high doses of statins (rosuvastatin 40/20 mg or atorvastatin 80 mg).^{43,44} Atorvastatin can improve the endothelial function using the enhanced expression of nitric oxide (NO), suppress the proliferation of smooth muscle cells and platelet aggregation, and reduce inflammation and oxidative stress.⁴⁵ Atorvastatin prevents the activation of an intrinsic apoptotic pathway in human kidney cells.⁴⁶ Also, atorvastatin could regulate kidney hypoperfusion after radiocontrast exposure by decreasing the expression of angiotensin receptors and endothelin-1 synthesis.^{47,48} Zhang *et al.*⁴⁹ conducted one of the primary meta-analyses including 4 trials and a total of 752 subjects and found that statin pretreatment had no significant role in preventing CI-AKI and, also, serum creatinine levels were fairly higher in patients treated with statins.

Multivariable analysis by Patti *et al.*⁵⁰ displayed that short-term pretreatment with high-dose atorvastatin load inhibited CIN and reduced hospital stay in patients with acute coronary syndrome undertaking PCI.

Quintavalle *et al.*⁴⁶ revealed that administration of a single high dose of atorvastatin (80 mg) within 24 hours before CM exposure was efficient in decreasing the rate of CI-AKI in patients with and without DM as well as in patients with moderate CKD; however, this procedure was not fruitful in patients with severe CKD.

Mc Donald *et al.*⁵¹ conducted a meta-analysis and confirmed that statins reduced the risk of CM-induced nephropathy.

In a small-randomized study (ROSA-CIN trial),

192 consecutive patients who experienced primary percutaneous intervention (p-PCI) through the diagnosis of ST-Elevation Myocardial Infarction (STEMI) were pretreated with high-dose rosuvastatin (40 mg) or atorvastatin (80 mg) and the results did not exhibit any differences in the rates of CIN.⁵² Also, preprocedural high-dose atorvastatin (80 mg) prevents CIN in patients with acute STEMI undertaking emergency PCI.⁵³

In the TRACK-D trial, the authors elaborated that rosuvastatin considerably decreased the risk of CI-AKI in patients with diabetes mellitus and CKD undertaking arterial contrast medium injection.⁵⁴

The results of meta-analysis by Barbieri *et al.*⁵⁵ exhibited that amongst the patients undertaking coronary angiography/percutaneous intervention, CIN occurred in 3.3 % of the patients treated with statins versus 6.4 % of the patients belonging to the placebo group; therefore, hydration with short-term statins decreased the incidence of CIN and was extremely suggested for patients with low LDL-cholesterol levels.⁵⁵

Another meta-analysis including 12 Randomized Controlled Trials (RCT) found that CI-AKI arose in 3.4% of the patients pretreated with high-dose statins and 7.6% of the patients in the low-dose.⁵⁶

Yang *et al.*⁵⁷ performed a meta-analysis of five RCTs and assessed the protective effects of rosuvastatin on CI-AKI. Patients treated with rosuvastatin had a 51% lower risk of CI-AKI and exhibited the reduced risk of Major Adverse Cardiovascular Events (MACEs).

Liu *et al.*⁵⁸ performed an updated meta-analysis including 9 RCTs and demonstrated that the patients undergoing coronary angiography/percutaneous interventions received statin therapy and exhibited a 53% lower risk of CIN than the control group.

Thirteen prospective RCTs conducted by Cheungpasitporn *et al.*⁵⁹ showed the significant protective effect of periprocedural statins on the incidence of CI-AKI and proposed hydration with statins along with standard IV crystalloid hydration in the prevention of CI-AKI.

Thompson *et al.*⁶⁰ performed a meta-analysis of 19 RCTs. The pooled analysis revealed a significant reduction in the incidence of CI-AKI in patients treated with statin before invasive angiography compared to the control group, while other studies enrolled a population of patients with a mean eGFR of < 60 mL/min/1.73 m² and did not show a significant reduction in CI-AKI with statin.

The significant conclusion of meta-analysis of 9 prospective randomized controlled studies implied that short-term high-dose statins could prevent CIN in patients with or without CKD regardless of the type of statins.⁶¹ There was no difference in renal function parameters between the short-term atorvastatin and the chronic statin therapy in patients undergoing elective coronary angiography.⁶²

One of the recent meta-analyses done by Liu *et al.*⁶³ included 9 RCTs and compared atorvastatin pretreatment with a low-dose statin in patients undergoing coronary angiography. The mentioned researchers illustrated that

pretreatment with a daily dose of ≥ 80 mg decreased the prevalence of CI-AKI significantly.

Sodium Bicarbonate vs. Statins for Prevention of CI-AKI

A short-term high-dose administration of atorvastatin before and after contrast exposure, along with standard intravenous hydration and oral N-acetylcysteine, do not reduce CA-AKI incidence in patients with pre-existing CKD.⁶⁴ Volume expansion with normal saline or sodium bicarbonate reinforces the attempt to prevent post-contrast acute kidney injuries; however, there is still indecisiveness about what the best protocol is.⁶⁵

Giacoppo *et al.*⁶⁶ completed a meta-analysis containing 124 trials and 28240 patients by comparing a total of 10 strategies. The risk of CI-AKI was decreased using statin (Odds ratio [OR], 0.42, 0.26–0.67), xanthine (OR, 0.32, 0.17–0.57), sodium bicarbonate (OR, 0.66, 0.47–0.90), N-acetylcysteine (OR, 0.68, 0.55–0.84), and N-acetylcysteine plus sodium bicarbonate (OR, 0.50, 0.33–0.76), compared to saline.^{67,68} In aggregate, these results highlight the important role of statin as the best treatment option in preventing CI-AKI in patients experiencing percutaneous coronary procedures with CM administration. N-acetylcysteine, sodium bicarbonate, and N-acetylcysteine

plus sodium bicarbonate administration might be linked to a mild CI-AKI risk decrease compared with saline.⁶⁶ A comparison of the efficacy of 12 treatment strategies employed for preventing CI-AKI including 150 trials showed that administering high doses of statin (comprised rosuvastatin (20–40 mg), simvastatin (40–80 mg), and atorvastatin (40–80 mg)) considering hydration with or without N-acetylcysteine might be the desired treatment approach to preventing CI-AKI in patients experiencing diagnostic and/or interventional procedures necessitating CM.⁶⁹ In the Bayesian network, meta-analysis of 49 RCT statins decreased the relative risk of CI-AKI compared with normal saline.⁷⁰ Subgroup analyses revealed that in patients receiving low osmolar contrast, statins decreased the relative risk of CI-AKI by 58% versus normal saline.⁷⁰

A comprehensive systematic review of the meta-analysis applied to the incidence of CIN was performed by Ali-Hasan-Al-Saegh *et al.*⁷¹ Pooled analysis indicated the beneficial effects of sodium bicarbonate versus normal saline ([OR] = 0.73, 0.56–0.94), N-acetylcysteine (OR = 0.79, 0.70–0.88), vitamin C (OR=0.64, 0.45–0.89), statins (OR= 0.45, 0.35–0.57), and angiotensin-converting enzyme inhibitors [ACEIs] (OR = 1.06, 0.69–1.61). Results of this study displayed that statins reduced the risk of CIAKI by 55% compared with placebo.⁷¹ The findings of the clinical

Table 1. Clinical trials in prevention of CA-AKI.

No.	Intervention (n)	Study design	Mean Baseline Serum (mg/dL)	Contrast volume (mL)	Ref.
1	-Patients with stable renal insufficiency -NaHCO ₃ group, n = 60 -NS group, n = 59	-As a bolus of 3 mL/kg per hour for 1 hour before iopamidol contrast, followed by an infusion of 1 mL/kg per hour for 6 hours after the procedure.	1.7	134	72
2	-Patients undergoing cardiovascular procedures. -NaHCO ₃ group, n = 88 -NS group, n = 88 -NAC + NS group, n = 88	-Infused at 1 mL/kg/h starting 6 hours before contrast administration, followed by a 1 mL/kg/h infusion for 6 hours after the procedure.	1.3	110	20
3	-RENO trial -Patients undergoing emergency percutaneous coronary intervention -NAC + NaHCO ₃ group, n = 56 -NS group, n = 55	-Administration before contrast injection and continued for 12 h after PCI.	1	285	21
4	-Patients exposed to nonionic iso-osmolar contrast medium iodixanol -NaHCO ₃ group, n = 71 -NS group, n = 74	-Fluids were administrated IV for 2 hours before, and 6 hours after administration of contrast medium.	1.6	135.7	22
5	-Patients with stable renal disease -Undergoing CAG -NaHCO ₃ group, n = 175 -NS group, n = 178	-Administered at 3 mL/kg for 1 hour before CAG, decreased to 1.5 mL/kg per hour during the procedure and for 4 hours after the completion of the procedure.	1.5	131.6	23
6	-Patients with CKD stage III–IV -NaHCO ₃ group, n = 51 -NS+ NAC, n = 42	-The first IV bolus was 3 mL/kg for 1 hour before the procedure, and 1 mL/kg/L for 6 hours after the procedure.	1.8	93	73
7	-Patients undergoing CAG -NaHCO ₃ + NS group, n = 135 -NS group, n = 130	-1 hour before contrast injection, followed by an infusion of 1 mL/kg/h for 6 hours after the procedure.	1.6	117.5	74

Table 1. Continued.

8	-Patients with mild renal insufficiency - NaHCO ₃ group, n = 72 -NS group, n = 72	-5 minutes before contrast exposure.	1.4	85	75
9	-Patients undergoing CAG or PCI -NaHCO ₃ group, n = 96 -NS group, n = 96	-Infused at 3 mL/kg/h starting 1 hour before contrast administration, followed by a 1 mL/kg/h infusion for 6 hours after the procedure.	1.1	63	17
10	-Patients undergoing CAG or PCI -NaHCO ₃ group, n = 52 -NS group, n = 51 -NS + NAC group, n = 53	-At a rate of 1 mL/kg BW/h for 12 hours before and 12 hours after contrast injection.	1.5	195	76
11	-Patients with CKD undergoing emergent procedures -NaHCO ₃ group, n = 30 -NS group, n = 29	-At the dose of 0.5 ml/kg, after hospital admitted, and 1 mL/kg/h during and for 6 hours after the procedure.	1.4	111	77
12	-Patients undergoing CAG -NaHCO ₃ group, n = 78 -NS group, n = 77	-Infused at 1 mL/kg/h continued from 3 hours before to 6 hours after the procedure.	1.5	135	78
13	-DM patients with impaired renal function undergoing endovascular angiography -PREVENT trial -NaHCO ₃ + NAC, n = 193 -NS + NAC group, n = 189	-At the rate of 3 mL/kg for 1 hour before contrast injection, followed by an infusion of 1 mg/kg/h during and 6 hours after the procedure.	1.5	116	79
14	-Patients undergoing cardiac catheterization -NaHCO ₃ group, n = 150 -NS group, n = 151	-Infused at 3 mL/kg/h starting 1 hour before contrast administration, followed by a 1 mL/kg/h infusion for 6 hours after the procedure.	1.5	124	28
15	-Patients with renal insufficiency undergoing intravascular contrast procedures - 7 h NaHCO ₃ group, n = 87 -Short-term NaHCO ₃ group, n = 82 - 24 h NS group, n = 89	-At least 12h prior and after the procedure or SB 3 mL/kg for 1h before and 1 mL/kg/h for 6h after the procedure or 3 mL/kg over 20 min before the procedure plus sodium bicarbonate orally (500 mg per 10 kg).	1.37	100	29
16	-DM patients with impaired renal function undergoing with use of low-osmolar contrast media -NaHCO ₃ group, n = 61 -NS group, n = 59	-Infusion 1 hour immediately before and for 6 hours following the intervention.	1.9	110	30
17	-Patients with ischemic heart disease undergoing CAG -NAC + NaHCO ₃ , n = 138 -NS group, n = 158	-Since 2 hours before the administration of contrast medium. The infusion prolonged for the following 6 hours after the procedure with an infusion rate of 1 mL/kg/h	1.5	-	80
18	-Patients with DM with unselected renal functions -NaHCO ₃ group, n = 94 -NS group, n = 101	-At 1 mL/kg/h starting 6 hours before contrast administration, followed by a 1 mL/kg/h infusion for 6 hours after the procedure.	1	90	81
19	-Patients with STEMI -CINSTEMI trial -NAC group n = 176 -NaHCO ₃ group, n = 181 -NAC + NaHCO ₃ group, n = 177 -NS group, n = 181	-In the 1 hour followed by infusion of 100 mL/h in the next 5 hours	0.85	140	82
20	-Patients undergoing coronary interventions -NAC + NaHCO ₃ group, n = 175 -NS+ NAC group, n = 175	-Fixed dose of fluid 6 hours before the procedure and 6 hours after it.	1.1	-	83
21	-Outpatients exposed to ioxitalamate during CAG and ventriculography -NaHCO ₃ +NS group, n = 126 -High dose of NS+ NAC group, n = 125 -NS group, n = 125	-From 1 hour before through 6 hours after exposure.	1.2	350	84

Table 1. Continued.

22	-Patients with CKD -NaHCO ₃ group, n=195 -NS group, n = 196	-Over 60 minutes before angiography and 1.5 mL/kg/h during and for 4 hours after angiography.	1.9	107	85
23	-Patients with moderate renal impairment undergoing cardiac catheterization -CONTRAST trial -NaHCO ₃ group, n=153 -NS+ NAC group, n = 157 -NaHCO ₃ + NAC group, n=156	-Starting from the day before angiography (to a total of 6 doses).	1.5	116	34
24	-Patients at high risk for renal complications -NaHCO ₃ group, n=2511 -NS group, n=2482 -NAC group, n=2495 -Placebo group, n=2498	-Receive IV 1.26% SB or NS and 5 days of oral NAC or oral placebo.	1.5	85	35
25	-Patients with chronic renal insufficiency undergoing CAG -PROMISS trial -Simvastatin group, n = 124 -Placebo group, n=123	-160 mg total, 40 mg orally every 12 hours starting the evening before and ending the morning after the procedure.	1.25	182	86
26	-Patients with CKD subjected to CAG or angioplasty -Atorvastatin group, n = 152 -Placebo group, n=152	-80 mg/d atorvastatin for 48 hours before and 48 hours after CM administration plus oral NAC 1200 mg twice daily.	1.2	159	11
27	-Patients undergoing CAG -Atorvastatin + NAC group, n = 60 -NAC group, n = 70	-80 mg atorvastatin plus 600 mg NAC twice daily in first day followed by 80 mg atorvastatin for 2 days after the procedure.	0.8	95	47
28	-Patients undergoing CAG -Atorvastatin group, n =80 -Placebo group, n=80	-40 mg/d atorvastatin started 3 days before CAG and continued for 48 hours after the procedure.	0.8	-	62
29	-Patients with acute coronary syndrome undergoing PCI ARMYDA-CIN trial -Atorvastatin group, n = 120 -Placebo group, n=121	-80 mg 12 hours before intervention with another 40-mg preprocedure dose.	1.04	211	50
30	-Patients with CKD -NAPLES II trial -Atorvastatin group, n = 202 - Placebo group, n=208	-80 mg atorvastatin within 24 hours before CM exposure plus NAC 1200 mg twice daily, orally the day before and day of CM administration. - All patients received a high dose of NAC and NaHCO ₃ solution	1.3	180.5	46
31	-Statin-naive patients with acute STEMI undergoing emergency PCI -Atorvastatin group, n =78 -NS group, n=83	-High-dose atorvastatin 80 mg followed by long-term atorvastatin (40 mg/day).	0.83	102	53
32	-Patients with type 2 DM and concomitant CKD undergoing coronary/peripheral arterial angiography -Rosuvastatin group, n = 1498 -NS group, n = 1500	-10 mg/d rosuvastatin for 5 days (2 days before and 3 days after the procedure).	1.07	115	54
33	-Patients with ACS -PRATO-ACS trial -Rosuvastatin group, n = 252 -Placebo group, n=252	-40 mg on admission, followed by 20 mg/day; plus 1200 mg NAC twice daily from the day before through the day after angiography.	0.95	144	87
34	-Statin-naive patients with CKD who underwent coronary or peripheral angiography -Rosuvastatin group, n = 110 -NS group, n = 110	-40 mg on admission, followed by 20 mg/day for 2 days.	1.35	128	88

Table 1. Continued.

35	-Patients referred for angiography -Atorvastatin group, n =100 -NS group, n=100	-80 mg oral atorvastatin 12 hours before contrast injection.	1.15	-	89
36	-Diabetic patients with renal dysfunction undergoing PCI -Atorvastatin group, n = 65 -Placebo group, n=65	-80 mg atorvastatin daily for 48 hours.	2	276	90

trials bent on preventing the occurrence of CA-AKI are summarized in Table 1.⁷²⁻⁹⁰

Conclusion

CA-AKI is one of the major complications of contrast injection for which preventive methods have always been considered. An optimal preventive strategy for CI-AKI remains unexplored and unassessed. Therefore, intravenous hydration and avoidance of high osmolar agents are the two approaches that consistently display a decrease in the risk of CI-AKI. Sodium bicarbonate was more effective than saline in preventing CI-AKI. Statins had the maximum possibility of decreasing the risk of CI-AKI, risk of hemodialysis, and all-cause mortality.

The benefit of adding an atorvastatin loading dose to the sodium bicarbonate solution and N-acetylcysteine seems to be effective in treating patients exposed to low to medium risks, but not in those with a high risk.

Future approaches include large-sized trials on the short-term effects of high-dose atorvastatin on preventing CI-AKI. Also, comprehensive multicenter trials are necessary to confirm whether sodium bicarbonate can prevent CI-AKI before routine use can be suggested. Future studies are also required to test the effects of combinations of different approaches, which have been revealed to be useful in this analysis, and to discover any possible potential mechanisms.

Author Contributions

SD analyzed data and wrote the manuscript. AM analyzed data and edited the final version of the manuscript. NG and SG collected data. HS designed and supervised the study and correspondence during the paper submission. All authors read and approved the final manuscript.

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Conflict of Interest

The authors report no conflicts of interest.

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