The following manuscript was accepted for publication in Pharmaceutical Sciences. It is assigned to an issue after technical editing, formatting for publication and author proofing

Citation: Dolati S, Mahmoodpoor A, Gharizadeh N, Gholipouri S, Soleimanpour H. Sodium bicarbonate versus statins to prevent contrast-induced acute kidney injury: A comprehensive review, Pharm Sci. 2021, doi: 10.34172/PS.2021.15

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

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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.

Keywords: Contrast media; Acute kidney injury; Hydration; Clinical Pharmacy; Sodium Bicarbonate; Statins.

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 ≥ 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.

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. 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.[22] Brar et al. conducted a randomized controlled study with a population of 353 patients undergoing coronary angiography.[23] 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.[25]

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.[30] 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 m^2 might be a safer strategy in patients receiving CM.[38]

Recently, Cai et al. 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.[39]

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-1synthesis.[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.[50]

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.

McDonald 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).[57]

Liu et al. performed an updated meta-analysis[58] 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.[58]

Thirteen prospective RCTs conducted by Cheungpasitporn et al. 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.[59]

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 m^2 and did not show a significant reduction in CI-AKI with statin.[60]

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.[66] 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 Sayegh 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 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 Contribution: Sanam Dolati and Ata Mahmoodpoor wrote the manuscript. Nafiseh Gharizadeh and Saina Gholipouri wrote some part of manuscript and edited final version and

drew the table. Hassan Soleimanpour designed and supervised the study, submitted the paper and correspondence during the paper submission.

Acknowledgments

The authors would like to thank Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran for their great help. The research protocol was approved and supported by Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran (grant number: 63716).

References

1. Gandhi S, Mosleh W, Abdel-Qadir H, Farkouh ME. Statins and contrast-induced acute kidney injury with coronary angiography. *Am J Med* 2014;127(10):987-1000. doi: 10.1016/j.amjmed.2014.05.011.
2. Lefel N, Janssen L, le Noble J, Foudraine N. Sodium bicarbonate prophylactic therapy in the prevention of contrast-induced nephropathy in patients admitted to the intensive care unit of a teaching hospital: a retrospective cohort study. *J Intensive Care* 2016;4(1):5. doi: 10.1186/s40560-016-0127-6.
3. Abouzeid SM, ElHossary HE. Na/K citrate versus sodium bicarbonate in prevention of contrast-induced nephropathy. *Saudi J Kidney Dis Transpl.* 2016;27(3):519.doi: 10.4103/1319-2442.182386.
4. Weisbord SD. Contrast-associated acute kidney injury. Core Concepts in Acute Kidney Injury: Springer; 1st ed. 2018 Edition. p. 95-112.
5. Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, et al. The definition of acute kidney injury and its use in practice. *Kidney Int* 2015;87(1):62-73. doi: 10.1038/ki.2014.328.
6. Hossain MA, Costanzo E, Cosentino J, Patel C, Qaisar H, Singh V, et al. Contrast-induced nephropathy: Pathophysiology, risk factors, and prevention. *Saudi J Kidney Dis Transpl* 2018;29(1):1. doi: 10.4103/1319-2442.225199.
7. Barbero U, Iannaccone M, De Benedictis M, Doronzo B. Contrast induced acute kidney injury and the role of beta-blockers in its prevention. *J Thorac Dis* 2019;11(7):2689. doi: 10.21037/jtd.2019.06.53.
8. Bangalore S. Statins for prevention of contrast-associated acute kidney injury: is the debate a moot point?. *Cardiovasc Revasc Med*. 2019;20:632-3. doi:doi.org/10.1016/j.carrev.2019.07.004.
9. Samadian F, Dalili N, Mahmoudieh L, Ziaei S. Contrast-induced nephropathy: Essentials and concerns. *Iran J Kidney Dis* 2018;12(3):135.
10. Buccheri D. Contrast Induced Nephropathy in Cardiology, Prevention and Treatment: A Systematic Review. *EC Cardiology* 2020;7:01-12.
11. Zhao SJ, Zhong ZS, Qi GX, Tian W. The efficacy of N-acetylcysteine plus sodium bicarbonate in the prevention of contrast-induced nephropathy after cardiac catheterization and percutaneous coronary intervention: a meta-analysis of randomized controlled trials. Int J Cardiol. 2016;221:251-9. doi: 10.1016/j.ijcard.2016.07.086.

12. Feng Y, Huang X, Li L, Chen Z. N-acetylcysteine versus ascorbic acid or N-acetylcysteine plus ascorbic acid in preventing contrast-induced nephropathy: A meta-analysis. *Nephrology* 2018;23(6):530-8. doi: 10.1111/nep.13068.
13. Vandenberghe W, Hoste E. Contrast-associated acute kidney injury: does it really exist, and if so, what to do about it? *F1000Research* 2019;8. doi: 10.12688/f1000research.16347.1.
14. Boccalandro F, Shreyder K, Harmon L, Dhindsa M, Fahim T, Sheikh S. Five-year follow-up of patients with radio-contrast-induced acute renal injury. Can intravenous sodium-bicarbonate improve long-term outcomes?. *Cardiovasc Revasc Med.* 2020;S1553-8389(20):30767-3. doi: 10.1016/j.carrev.2020.11.017.
15. Briasoulis A, Pala M, Telila T, Merid O, Akintoye E, Vogiatzi G, Oikonomou E, Tousoulis D. Statins and contrast-induced nephropathy: a systematic review and meta-analysis. *Curr Pharm Des.* 2017;23(46):7141-8. doi: 10.2174/1381612823666170913170527.
16. Jang J-S, Jin H-Y, Seo J-S, Yang T-H, Kim D-K, Kim TH, et al. Sodium bicarbonate therapy for the prevention of contrast-induced acute kidney injury. *Circ J* 2012;76(9):2255-65. doi: 10.1253/circj.cj-12-0096.
17. Pakfetrat M, Nikoo MH, Malekmakan L, Tabandeh M, Roozbeh J, Nasab MH, et al. A comparison of sodium bicarbonate infusion versus normal saline infusion and its combination with oral acetazolamide for prevention of contrast-induced nephropathy: a randomized, double-blind trial. *Int Urol Nephrol* 2009;41(3):629. doi: 10.1007/s11255-008-9520-y.
18. Masuda M, Yamada T, Mine T, Morita T, Tamaki S, Tsukamoto Y, et al. Comparison of usefulness of sodium bicarbonate versus sodium chloride to prevent contrast-induced nephropathy in patients undergoing an emergent coronary procedure. Am J Cardiol 2007;100(5):781-6. doi: 10.1016/j.amjcard.2007.03.098.
19. O'sullivan S, Healy D, Moloney MC, Grace P, Walsh S. The role of N--acetylcysteine in the prevention of contrast-induced nephropathy in patients undergoing peripheral angiography: a structured review and meta-analysis. *Angiology* 2013;64(8):576-82. doi: 10.1177/0003319712467223.
20. Toso A, Leoncini M, Maioli M, Bellandi F. Pharmacologic Prophylaxis of Contrast-Induced Nephropathy. Interv Cardiol Clin. 2020 Jul;9(3):369-383. doi: 10.1016/j.iccl.2020.02.006.
21. Recio-Mayoral A, Chaparro M, Prado B, Cózar R, Méndez I, Banerjee D, et al. The reno-protective effect of hydration with sodium bicarbonate plus N-acetylcysteine in patients undergoing emergency percutaneous coronary intervention: the RENO Study. *J Am Coll Cardiol* 2007;49(12):1283-8. doi: 10.1016/j.jacc.2006.11.034.
22. Adolph E, Holdt-Lehmann B, Chatterjee T, Paschka S, Prott A, Schneider H, et al. Renal Insufficiency Following Radiocontrast Exposure Trial (REINFORCE): a randomized comparison of sodium bicarbonate versus sodium chloride hydration for the prevention of contrast-induced nephropathy. *Coron Artery Dis* 2008;19(6):413-9. doi: 10.1097/MCA.0b013e3283021ac6.
23. Brar SS, Shen AY-J, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium–induced nephropathy in patients undergoing coronary angiography: a randomized trial. Jama 2008;300(9):1038-46. doi: 10.1001/jama.300.9.1038.
24. Dong Y, Zhang B, Liang L, Lian Z, Liu J, Liang C, Zhang S. How strong is the evidence for sodium bicarbonate to prevent contrast-induced acute kidney injury after coronary angiography and percutaneous coronary intervention? *Medicine (Baltimore).* 2016 Feb;95(7):e2715. doi: 10.1097/MD.0000000000002715.
25. Hoste EA, De Waele JJ, Gevaert SA, Uchino S, Kellum JA. Sodium bicarbonate for prevention of contrast-induced acute kidney injury: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2010;25(3):747-58. doi: 10.1093/ndt/gfp389.
26. Briguori C, Visconti G, Focaccio A, Airoldi F, Valgimigli M, Sangiorgi GM, et al. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II) RenalGuard System in High-Risk Patients for Contrast-

Induced Acute Kidney Injury. *Circulation* 2011;124(11):1260-9. doi: 10.1161/CIRCULATIONAHA.111.030759.
27. Briguori C, Visconti G, Donahue M, De Micco F, Focaccio A, Golia B, et al. RenalGuard system in high-risk patients for contrast-induced acute kidney injury. *Am Heart J* 2016;173:67-76. doi: 10.1016/j.ahj.2015.12.005.
28. Gomes VO, Lasevitch R, Lima VC, Brito Jr FS, Perez-Alva JC, Moulin B, et al. Hydration with sodium bicarbonate does not prevent contrast nephropathy: a multicenter clinical trial. *Arq Bras Cardiol* 2012;99(6):1129-34. doi: 10.1590/s0066-782x2012005000108.
29. Klima T, Christ A, Marana I, Kalbermatter S, Uthoff H, Burri E, et al. Sodium chloride vs. sodium bicarbonate for the prevention of contrast medium-induced nephropathy: a randomized controlled trial. *Eur Heart J* 2012;33(16):2071-9. doi: 10.1093/eurheartj/ehr501.
30. Boucek P, Havrdova T, Oliyarnyk O, Skibova J, Pecenkova V, Pucelikova T, et al. Prevention of contrast-induced nephropathy in diabetic patients with impaired renal function: a randomized, double blind trial of sodium bicarbonate versus sodium chloride-based hydration. *Diabetes Res Clin Pract* 2013;101(3):303-8. doi: 10.1016/j.diabres.2013.05.015.
31. Kama A, Yılmaz S, Yaka E, Dervişoğlu E, Özgür Doğan N, Erimşah E, et al. Comparison of Short-term Infusion Regimens of N-Acetylcysteine Plus Intravenous Fluids, Sodium Bicarbonate Plus Intravenous Fluids, and Intravenous Fluids Alone for Prevention of Contrast-induced Nephropathy in the Emergency Department. *Acad Emerg Med* 2014;21(6):615-22. doi: 10.1111/acem.12400.
32. Kooiman J, Sijpkens YW, van Buren M, Groeneveld J, Ramai S, van der Molen AJ, et al. Randomised trial of no hydration vs. sodium bicarbonate hydration in patients with chronic kidney disease undergoing acute computed tomography–pulmonary angiography. *J Thromb Haemost* . 2014;12(10):1658-66. doi: 10.1111/jth.12701.
33. Kooiman J, de Vries J-PP, Van der Heyden J, Sijpkens YW, van Dijkman PR, Wever JJ, et al. Randomized Trial of 1-hour Sodium Bicarbonate Vs. Standard Saline Hydration in Patients With Chronic Kidney Disease Undergoing Intra-arterial Contrast Administration. *Circulation* 2014;130(suppl_2):A17645-A.
34. Chong E, Poh K-K, Lu Q, Zhang JJ-J, Tan N, Hou XM, et al. Comparison of combination therapy of high-dose oral N-acetylcysteine and intravenous sodium bicarbonate hydration with individual therapies in the reduction of Contrast-induced Nephropathy during Cardiac Catheterisation and Percutaneous Coronary Intervention (CONTRAST): a multi-centre, randomised, controlled trial. *Int J Cardiol* 2015;201:237-42. doi: 10.1016/j.ijcard.2015.07.108.
35. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin S-S, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med* 2018;378(7):603-14. doi: 10.1056/NEJMoa1710933.
36. Valette X, Desmeulles I, Savary B, Masson R, Seguin A, Sauneuf B, et al. Sodium bicarbonate versus sodium chloride for preventing contrast-associated acute kidney injury in critically ill patients: a randomized controlled trial. *Crit Care Med* 2017;45(4):637-44. doi: 10.1097/CCM.0000000000002267.
37. Pakfetrat M, Malekmakan L, Salmanpour Z, Nikoo MH, Izadpanah P. Comparison of normal saline, ringer's lactate, and sodium bicarbonate for prevention of contrast-induced nephropathy in patients with coronary angiography: A randomized double-blind clinical trial. *Indian J Nephrol* . 2019;29(1):22. doi: 10.4103/ijn.IJN_48_17.
38. Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, et al. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. *The Lancet* 2017;389(10076):1312-22. doi: 10.1016/S0140-6736(17)30057-0.
39. Cai Q, Jing R, Zhang W, Tang Y, Li X, Liu T. Hydration Strategies for Preventing Contrast-Induced Acute Kidney Injury: A Systematic Review and Bayesian Network Meta-Analysis. *J Interv Cardiol*

2020;2020. doi: 10.1155/2020/7292675.
40. Wong PCY, Li Z, Guo J, Zhang A. Pathophysiology of contrast-induced nephropathy. *Int J Cardiol* .2012;158(2):186-92. doi: 10.1016/j.ijcard.2011.06.115.
41. Zhang T, Shen L-H, Hu L-H, He B. Statins for the prevention of contrast-induced nephropathy: a systematic review and meta-analysis. *Am J Nephrol* 2011;33(4):344-51. doi: 10.1159/000326269.
42. Zhou X, Dai J, Xu X, Wang Z, Xu H, Chen J, Qiu Y, Mao W. Comparative efficacy of statins for prevention of contrast-induced acute kidney injury in patients with chronic kidney disease: a network meta-analysis. *Angiology*. 2019 Apr;70(4):305-316. doi: 10.1177/0003319718801246.
43. Eapci I, Eacts MS-u, Ahlsson A, Uk APB, Benedetto U, Germany RAB, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for. *G Ital Cardiol (Rome).* 2019 Jul-Aug;20(7-8 Suppl 1):1S-61S. doi: 10.1714/3203.31801.
44. Andreucci M, Faga T, Sabbatini M, Pisani A, Russo D, Michael A. How to prevent Contrast-Induced Nephropathy in clinical practice. *J Clin Nephrol Res* 2014;1(1):1002.
45. Ferreira TS, Lanzetti M, Barroso MV, Rueff-Barroso CR, Benjamim CF, de Brito-Gitirana L, et al. Oxidative stress and inflammation are differentially affected by atorvastatin, pravastatin, rosuvastatin, and simvastatin on lungs from mice exposed to cigarette smoke. *Inflammation* 2014;37(5):1355-65. doi: 10.1007/s10753-014-9860-y.
46. Quintavalle C, Fiore D, De Micco F, Visconti G, Focaccio A, Golia B, et al. Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. *Circulation* 2012;126(25):3008-16. doi: 10.1161/CIRCULATIONAHA.112.103317.
47. Katsiki N, Fonseca V, Mikhailidis DP. Contrast-induced acute kidney injury in diabetes mellitus: Clinical relevance and predisposing factors. Could statins be of benefit?. J Diabetes Complications. 2018;32(11):982-984. doi: 10.1016/j.jdiacomp.2018.08.008.
48. Chung YH, Lee YC, Chang CH, Lin MS, Lin JW, Lai MS. Statins of high versus low cholesterol-lowering efficacy and the development of severe renal failure. *Pharmacoepidemiol Drug Saf* 2013;22(6):583-92. doi: 10.1002/pds.3433.
49. Zhang L, Zhang L, Lu Y, Wu B, Zhang S, Jiang H, et al. Efficacy of statin pretreatment for the prevention of contrast-induced nephropathy: a meta-analysis of randomised controlled trials. Int J Clin Pract 2011;65(5):624-30. doi: 10.1111/j.1742-1241.2010.02588.x.
50. Patti G, Ricottini E, Nusca A, Colonna G, Pasceri V, D'Ambrosio A, et al. Short-term, high-dose Atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [atorvastatin for reduction of myocardial damage during angioplasty–contrast-induced nephropathy] trial. *Am J Cardiol* 2011;108(1):1-7. doi: 10.1016/j.amjcard.2011.03.001.
51. McDonald JS, McDonald RJ, Comin J, Williamson EE, Katzberg RW, Murad MH, et al. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. *Radiology* 2013;267(1):119-28. doi: 10.1148/radiol.12121460.
52. Kaya A, Kurt M, Tanboga IH, Işik T, Ekinci M, Aksakal E, et al. Ros uvastatin versus A torvastatin to prevent C ontrast I nduced N ephropathy in patients undergoing primary percutaneous coronary intervention (ROSA-CIN trial). *Acta Cardiol.* 2013;68(5):489-94. doi: 10.1080/ac.68.5.2994472.
53. Li W, Fu X, Wang Y, Li X, Yang Z, Wang X, et al. Beneficial effects of high-dose atorvastatin pretreatment on renal function in patients with acute ST-segment elevation myocardial infarction undergoing emergency percutaneous coronary intervention. *Cardiology* 2012;122(3):195-202. doi: 10.1159/000339472.

54. Han Y, Zhu G, Han L, Hou F, Huang W, Liu H, et al. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. *J Am Coll Cardiol* 2014;63(1):62-70. doi: 10.1016/j.jacc.2013.09.017.
55. Barbieri L, Verdoia M, Schaffer A, Nardin M, Marino P, De Luca G. The role of statins in the prevention of contrast induced nephropathy: a meta-analysis of 8 randomized trials. *J Thromb Thrombolysis* 2014;38(4):493-502. doi: 10.1007/s11239-014-1076-3.
56. Ukaigwe A, Karmacharya P, Mahmood M, Pathak R, Aryal MR, Jalota L, et al. Meta-analysis on efficacy of statins for prevention of contrast-induced acute kidney injury in patients undergoing coronary angiography. *Am J Cardiol* 2014;114(9):1295-302. doi: 10.1016/j.amjcard.2014.07.059.
57. Yang Y, Wu Y-x, Hu Y-z. Rosuvastatin treatment for preventing contrast-induced acute kidney injury after cardiac catheterization: a meta-analysis of randomized controlled trials. *Medicine* 2015;94(30). doi: 10.1097/MD.0000000000001226.
58. Liu Y-h, Liu Y, Duan C-y, Tan N, Chen J-y, Zhou Y-l, et al. Statins for the prevention of contrast-induced nephropathy after coronary angiography/percutaneous interventions: a meta-analysis of randomized controlled trials. *J Cardiovasc Pharmacol Ther* 2015;20(2):181-92. doi: doi.org/10.1177/1074248414549462.
59. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Edmonds PJ, O'Corragain OA, Srivali N, et al. Periprocedural effects of statins on the incidence of contrast-induced acute kidney injury: a systematic review and meta-analysis of randomized controlled trials. *Ren Fail* .2015;37(4):664-71. doi: 10.3109/0886022X.2015.1010939.
60. Thompson K, Razi R, Lee MS, Shen A, Stone GW, Hiremath S, et al. Statin use prior to angiography for the prevention of contrast-induced acute kidney injury: a meta-analysis of 19 randomised trials. *EuroIntervention* 2016;12(3):366-74. doi: 10.4244/EIJY15M05_03.
61. Briasoulis A, Mallikethi-Reddy S, Sharma S, Briasouli AA, Afonso L. 3-Hydroxy-3-methylglutaryl-CoA reductase enzyme inhibitors for prevention of contrast-induced nephropathy: a meta-analysis of prospective randomized controlled studies. *Am J Ther* 2015;22(6):e158-e66. doi: 10.1097/MJT.0000000000000126.
62. Acikel S, Muderrisoglu H, Yildirir A, Aydinalp A, Sade E, Bayraktar N, et al. Prevention of contrast-induced impairment of renal function by short-term or long-term statin therapy in patients undergoing elective coronary angiography. *Blood Coagul Fibrinolysis* 2010;21(8):750-7. doi: 10.1097/MBC.0b013e32834014a4.
63. Liu L-Y, Liu Y, Wu M-Y, Sun Y-Y, Ma F-Z. Efficacy of atorvastatin on the prevention of contrast-induced acute kidney injury: a meta-analysis. *Drug Des Devel Ther* 2018;12:437. doi: 10.2147/DDDT.S149106.
64. Sreenivasan J, Khan MS, Li H, Zhuo M, Patel A, Fugar S, Tarbutton M, Siddamsetti S, Yadav N. Statins and incidence of contrast-induced acute kidney injury following coronary angiography-Five year experience at a tertiary care center. Cardiovasc Revasc Med. 2019;20(8):654-658. doi: 10.1016/j.carrev.2018.09.012.
65. van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin M-F, Bertolotto M, et al. Post-contrast acute kidney injury. Part 2: risk stratification, role of hydration and other prophylactic measures, patients taking metformin and chronic dialysis patients. *Eur Radiol* 2018;28(7):2856-69. doi: 10.1007/s00330-017-5247-4.
66. Giacoppo D, Gargiulo G, Buccheri S, Aruta P, Byrne RA, Cassese S, et al. Preventive strategies for contrast-induced acute kidney injury in patients undergoing percutaneous coronary procedures: evidence from a hierarchical Bayesian network meta-analysis of 124 trials and 28 240 patients. *Circ Cardiovasc Interv* 2017;10(5):e004383. doi: 10.1161/CIRCINTERVENTIONS.116.004383.
67. Wood WG, Igbavboa U, Muller WE, Eckert GP. Statins, Bcl-2, and apoptosis: cell death or cell protection? *Mol Neurobiol* 2013;48(2):308-14. doi: 10.1007/s12035-013-8496-5.

68. Toso A, Leoncini M, Maioli M, Tropeano F, Di Vincenzo E, Villani S, et al. Relationship between inflammation and benefits of early high-dose rosuvastatin on contrast-induced nephropathy in patients with acute coronary syndrome: the pathophysiological link in the PRATO-ACS study (Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Nephropathy and Myocardial Damage in Patients With Acute Coronary Syndrome Undergoing Coronary Intervention). *JACC Cardiovasc Interv* 2014;7(12):1421-9. doi: 10.1016/j.jcin.2014.06.023.
69. Su X, Xie X, Liu L, Lv J, Song F, Perkovic V, et al. Comparative effectiveness of 12 treatment strategies for preventing contrast-induced acute kidney injury: a systematic review and Bayesian network meta-analysis. *Am J Kidney Dis* 2017;69(1):69-77. doi: 10.1053/j.ajkd.2016.07.033.
70. Khan SU, Khan MU, Rahman H, Khan MS, Riaz H, Novak M, et al. A Bayesian network meta-analysis of preventive strategies for contrast-induced nephropathy after cardiac catheterization. *Cardiovasc Revasc Med* 2019;20(1):29-37. doi: 10.1016/j.carrev.2018.06.005.
71. Ali-Hassan-Sayegh S, Mirhosseini SJ, Ghodratipour Z, Sarrafan-Chaharsoughi Z, Rahimizadeh E, Karimi-Bondarabadi AA, et al. Strategies preventing contrast-induced nephropathy after coronary angiography: a comprehensive meta-analysis and systematic review of 125 randomized controlled trials. *Angiology* 2017;68(5):389-413. doi: 10.1177/0003319716661445.
72. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *Jama* 2004;291(19):2328-34. doi: 10.1001/jama.291.19.2328.
73. Hagikura A, Goto K, Takebayashi H, Kikuta Y, Kobayashi K, Sato K, Taniguchi M, Hiramatsu S, Kawai Y, Kohno H, Kusuyama T. The role of saline and sodium bicarbonate preprocedural hydration to prevent mid-term renal insufficiency in patients with chronic kidney disease undergoing percutaneous coronary intervention. *Intern Med.* 2019 Apr 15;58(8):1057-1065. doi: 10.2169/internalmedicine.1442-18.
74. Vasheghani-Farahani A, Sadigh G, Kassaian SE, Khatami SMR, Fotouhi A, Razavi SAH, et al. Sodium bicarbonate plus isotonic saline versus saline for prevention of contrast-induced nephropathy in patients undergoing coronary angiography: a randomized controlled trial. *Am J Kidney Dis* 2009;54(4):610-8. doi: 10.1053/j.ajkd.2009.05.016.
75. Tamura A, Goto Y, Miyamoto K, Naono S, Kawano Y, Kotoku M, et al. Efficacy of single-bolus administration of sodium bicarbonate to prevent contrast-induced nephropathy in patients with mild renal insufficiency undergoing an elective coronary procedure. *Am J Cardiol* 2009;104(7):921-5. doi: 10.1016/j.amjcard.2009.05.034.
76. Castini D, Lucreziotti S, Bosotti L, Salerno Uriarte D, Sponzilli C, Verzoni A, et al. Prevention of contrast-induced nephropathy: a single center randomized study. *Clin Cardiol* 2010;33(3):E63-E8. doi: 10.1002/clc.20576.
77. Ueda H, Yamada T, Masuda M, Okuyama Y, Morita T, Furukawa Y, et al. Prevention of contrast-induced nephropathy by bolus injection of sodium bicarbonate in patients with chronic kidney disease undergoing emergent coronary procedures. *Am J Cardiol* 2011;107(8):1163-7. doi: 10.1016/j.amjcard.2010.12.012.
78. Kooiman J, de Vries JP, Van der Heyden J, Sijpkens YW, van Dijkman PR, Wever JJ, van Overhagen H, Vahl AC, Aarts N, Verberk-Jonkers IJ, Brulez HF. Randomized trial of one-hour sodium bicarbonate vs standard periprocedural saline hydration in chronic kidney disease patients undergoing cardiovascular contrast procedures. *PloS one*. 2018;13(2):e0189372. doi:10.1371/journal.pone.0189372.
79. Lee S-W, Kim W-J, Kim Y-H, Park S-W, Park D-W, Yun S-C, et al. Preventive strategies of renal insufficiency in patients with diabetes undergoing intervention or arteriography (the PREVENT Trial). *Am J Cardiol* 2011;107(10):1447-52. doi: 10.1016/j.amjcard.2011.01.019.
80. Alessandri N, Lanzi L, Garante C, Tersigni F, Sergiacomi R, Petrassi M, et al. Prevention of acute renal failure post-contrast imaging in cardiology: a randomized study. *Eur Rev Med Pharmacol Sci* 2013;17(Suppl 1):13-21. PMID: 23436661

81. Koc F, Ozdemir K, Altunkas F, Celik A, Dogdu O, Karayakali M, et al. Sodium bicarbonate versus isotonic saline for the prevention of contrast-induced nephropathy in patients with diabetes mellitus undergoing coronary angiography and/or intervention: a multicenter prospective randomized study. *J Investig Med* 2013;61(5):872-7. doi: 10.2310/JIM.0b013e31828e9cab.
82. Thayssen P, Lassen JF, Jensen SE, Hansen KN, Hansen HS, Christiansen EH, et al. Prevention of contrast-induced nephropathy with N-acetylcysteine or sodium bicarbonate in patients with ST-segment–myocardial infarction: A prospective, randomized, open-labeled trial. *Circ Cardiovasc Interv* 2014;7(2):216-24. doi: 10.1161/CIRCINTERVENTIONS.113.000653.
83. Mahmoodi K, Sohrabi B, Ilkhchooyi F, Malaki M, Khaniani ME, Hemmati M. The efficacy of hydration with normal saline versus hydration with sodium bicarbonate in the prevention of contrast-induced nephropathy. *Heart views* 2014;15(2):33. doi: 10.4103/1995-705X.137489.
84. Inda-Filho AJ, Caixeta A, Manggini M, Schor N. Do intravenous N-acetylcysteine and sodium bicarbonate prevent high osmolal contrast-induced acute kidney injury? A randomized controlled trial. *PloS one* 2014;9(9). doi: 10.1371/journal.pone.0107602. eCollection 2014.
85. Solomon R, Gordon P, Manoukian SV, Abbott JD, Kereiakes DJ, Jeremias A, et al. Randomized trial of bicarbonate or saline study for the prevention of contrast-induced nephropathy in patients with CKD. *Clin J Am Soc Nephrol* 2015;10(9):1519-24. doi: 10.2215/CJN.05370514. Epub 2015 Jul 16.
86. Jo S-H, Koo B-K, Park J-S, Kang H-J, Cho Y-S, Kim Y-J, et al. Prevention of radiocontrast medium–induced nephropathy using short-term high-dose simvastatin in patients with renal insufficiency undergoing coronary angiography (PROMISS) trial—a randomized controlled study. *Am Heart J* 2008;155(3):499. e1-. e8. doi: 10.1016/j.ahj.2007.11.042.
87. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. et al. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: Results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome). *J Am Coll Cardiol* 2014;63(1):71-9. doi: 10.1016/j.jacc.2013.04.105.
88. Abaci O, Ozkan AA, Kocas C, Cetinkal G, Karaca OS, Baydar O, et al. Impact of rosuvastatin on contrast-induced acute kidney injury in patients at high risk for nephropathy undergoing elective angiography. *Am J Cardiol*. 2015;115(7):867-71. doi: 10.1016/j.amjcard.2015.01.007.
89. Bidram P, Roghani F, Sanei H, Hedayati Z, Golabchi A, Mousavi M, et al. Atorvastatin and prevention of contrast induced nephropathy following coronary angiography. *J Res Med Sci* . 2015;20(1):1. PMID: 25767514
90. Shehata M, Hamza MJCt. Impact of high loading dose of atorvastatin in diabetic patients with renal dysfunction undergoing elective percutaneous coronary intervention: a randomized controlled trial. *Cardiovasc Ther* . 2015;33(2):35-41. doi: 10.1111/1755-5922.12108.

Table. 1. Clinical trials in prevention of CA-AKI.					
	Intervention (n)	Study design	Mean Baseline Serum(mg/dL)	Contrast volume (mL)	References
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]
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	1.1	63	[17]

		infusion for 6 hours after the procedure.			
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	-At 1 mL/kg/h starting 6 hours before contrast administration, followed	1	90	[81]

	-NS group, n = 101	by a 1 mL/kg/h infusion for 6 hours after the procedure.			
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]
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	0.8	95	[47]

		mg atorvastatin for 2 days after the procedure.			
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
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