

# Protective effect of allopurinol in preventing contrast-induced nephropathy among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis

Kanaan Mansoor<sup>1</sup>, Mohamed Suliman<sup>1</sup>, Mohammad Amro<sup>2</sup>, Saad Malik<sup>1</sup>, Ahmad Amro<sup>1</sup>, Zachary Curtis<sup>1</sup>, Mehiar El-Hamdani<sup>1</sup>, Iheanyichukwu Ogu<sup>1</sup>, Wilbert S. Aronow<sup>3</sup>

<sup>1</sup>Marshall University, Huntington, USA

<sup>2</sup>Misr University for Science and Technology, Egypt

<sup>3</sup>Westchester Medical Center and New York Medical College, Valhalla, NY, USA

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**Corresponding author:**

Dr. Mohamed Suliman

Marshall University

Huntington, WV

25701, USA

E-mail: [mssuliman@gmail.com](mailto:mssuliman@gmail.com)

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## Abstract

**Introduction:** Contrast-induced nephropathy (CIN) is the third most common cause of iatrogenic acute renal failure and is triggered by administration of radiopaque contrast media. Periprocedural hydration is imperative in prevention of CIN, and uric acid has been recognized to have an integral role in development of renal disease. The aim of our study is to understand the efficacy of allopurinol in preventing CIN among patients undergoing percutaneous coronary intervention.

**Material and methods:** A literature search was performed on PubMed (Medline), Science Direct and Cochrane Library using a combination of Mesh terms. We limited our search to randomized controlled trials (RCTs) and articles published in the English language. The PRISMA protocol was utilized to conduct this meta-analysis.

**Results:** Six studies were included in the final analysis. All included studies were clinical trials conducted between 2013 and 2019. A total of 853 patients were included. There was a significant reduction in the risk of CIN among patients who were pretreated with adequate hydration plus allopurinol (100 to 600 mg) compared to hydration only before undergoing percutaneous coronary angiography (RR = 0.39, 95% CI: 0.21–0.73). A sensitivity analysis of studies using 300 mg of allopurinol only reported a significant reduction in CI-AKI compared to hydration alone (RR = 0.26, 95% CI: 0.11–0.57).

**Conclusions:** Our study demonstrates that Allopurinol is effective in preventing contrast-induced nephropathy in patients undergoing percutaneous coronary intervention. Larger clinical trials are warranted to better understand this effect.

**Key words:** contrast-induced nephropathy, allopurinol, percutaneous coronary intervention, coronary artery disease, acute kidney injury.

## Introduction

Contrast-induced nephropathy (CIN) was first described in 1954, which occurred after intravenous pyelography [1]. CIN is the third most common cause of iatrogenic acute renal failure [2]. A prospective study by Hou *et al.*

on iatrogenic renal insufficiency revealed around 79% of cases occurring from decreased renal perfusion, post-operative insufficiency, radiographic contrast media and aminoglycosides. Risk factors for developing CIN are age, diabetes mellitus, chronic kidney disease, volume of contrast media, congestive heart failure, cardiogenic shock and history of renal transplant [3]. The accepted definition of CIN is a 25% relative increase or an absolute increase of 0.5 mg/dl in creatinine levels within 48–72 h of contrast exposure, in the absence of other causation [2–4]. The burden of CIN is rising due to increasing frequency of contrast-dependent radiologic imaging and therapeutic interventional studies [2]. As a result of the paradigm shift in the treatment of structural heart disease and stable ischemic heart disease, there has been a substantial increase in the number of percutaneous interventions for many debilitated patients as in transcatheter aortic valve replacement (TAVR) for severe aortic stenosis, Mitra Clip for mitral regurgitation and percutaneous coronary intervention (PCI) for chronically totally occluded (CTO) coronary arteries. These complex percutaneous interventions have resulted in increasing procedure time and contrast amount used, which inadvertently leads to a significant increase in the incidence of CIN. CIN is known to affect as many as 50% of the high risk patients who undergo coronary angiography or percutaneous coronary intervention [2, 3]. In addition to prolonging hospital stay, CIN is associated with an overall increase in mortality with a dramatic increase of in-hospital mortality up to 5 times [5, 6].

In an effort to counter the effect of contrast media on renal function, multiple preventative strategies have been recommended. Current evi-

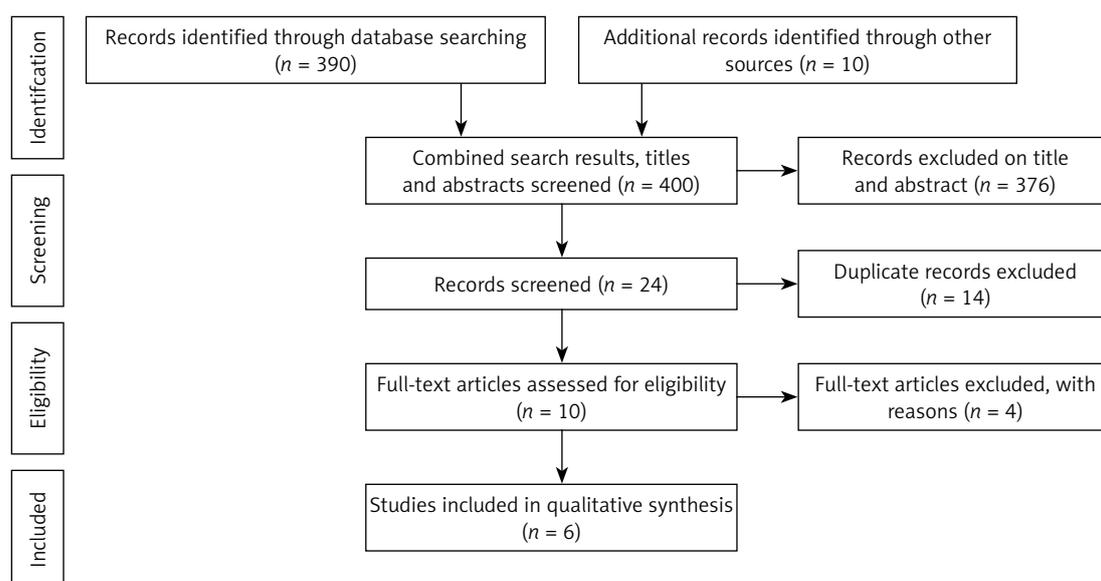
dence for employing pharmaceutical intervention to prevent CIN is inconsistent and warrants further prospective studies. In 2014 the European Society of Cardiology (ESC) recommended the use of the minimal possible volume of contrast media to prevent CIN. In addition, periprocedural hydration is imperative in prevention of CIN as recommended by the ESC [7]. In recent literature, uric acid has been implicated in the development of renal disease as well as CIN, which led many studies to investigate the efficacy of allopurinol in preventing CIN [8, 9]. Allopurinol is a competitive inhibitor of xanthine oxidase (XO) which is used to treat hyperuricemia; it also inhibits the production of free radicals that are a potential cause of CIN [4].

The aim of our study is to understand the efficacy of allopurinol in preventing CIN among patients undergoing percutaneous coronary intervention.

## Material and methods

We performed a literature search on PubMed (MEDLINE), Science Direct and Cochrane Library using a combination of MeSH terms and keywords which included contrast-induced injury, acute kidney injury, allopurinol, percutaneous coronary intervention, contrast medium and coronary angiography. We limited our search to randomized control trials (RCTs) and articles published in the English language. The PRISMA (Preferred Reporting Items for Systemic Review and Meta-Analysis) protocol was utilized to conduct this meta-analysis (Figure 1) [10].

A total of 400 titles and abstracts were reviewed, up to the date of 12/30/2019. All literature was tabulated in Mendeley citation manager.



**Figure 1.** PRISMA diagram showing screening process starting from titles retrieved at initial literature search, reasons of exclusion and total articles included in final quantitative analysis

**Table I.** Inclusion and exclusion criteria, used by the studies in our meta-analysis, to recruit eligible patients for assessing the effect of contrast-induced nephropathy after percutaneous cardiac intervention

Authors/year	Exclusion	Inclusion	Definition of CIN
Erol <i>et al.</i> /2013	Patients with acute myocardial infarction (AMI), cardiogenic shock, acute renal failure, current peritoneal dialysis or hemodialysis, planned post-contrast dialysis, history of intravascular administration of contrast agents or anticipated re-administration of contrast agents within the following 4 days	Patients with stable serum creatinine levels $\geq 1.1$ mg/dl	An increase in baseline serum creatinine concentration by 25%
Kumar <i>et al.</i> /2014	Patients who received more than the maximum permissible dose of the dye, patients on any nephrotoxic drugs, patients with gout or serum uric acid levels $> 10$ mg/dl, history of hypersensitivity or intolerance to allopurinol, congestive heart failure or ejection fraction $< 40\%$ and inability to give consent	Patients undergoing angiography or angioplasty with stable creatinine	A rise in serum creatinine levels of 0.5 mg/dl, or a 25% increase from baseline
Ghelich <i>et al.</i> /2017	Patients with acute coronary syndrome, CABG/PPCI, patients with a history of allopurinol use, gout, SCr $> 3$ mg/dl or eGFR $< 60$ ml/min, hepatic failure, 6MP, warfarin, azathioprine, history of allergy to allopurinol	eGFR $> 60$ ml/min	A 25% increase in serum cystatin C relative to the patient's baseline value in the first 24 h
Sadineni <i>et al.</i> /2017	Patients with acute renal failure, end stage renal disease requiring dialysis, recent history of intravascular administration of contrast material within previous 6 days, pregnancy, lactation, emergent coronary angiography, history of hypersensitivity reaction to contrast media, cardiogenic shock, pulmonary edema, mechanical ventilator, parenteral use of diuretics, recent use of NAC, recent use of ascorbic acid, and use of metformin or NSAIDs within 48 h of procedure were excluded from the study	Patients with age more than 30 years and a stable serum creatinine of $\geq 1.2$ mg/dl	An increase in serum creatinine from baseline of $\geq 25\%$ or an absolute increase of $\geq 0.3$
Iranirad <i>et al.</i> /2017	Patients with end-stage renal insufficiency (eGFR less than 15 ml/min), acute renal insufficiency, pregnancy and lactation, pulmonary edema, cardiogenic shock, multiple myeloma, history of an allergic reaction to contrast agents or allopurinol, contrast media exposure within seven days before the procedure, uremia, renal failure resulting in receiving dialysis and the administration of NAC, metformin, dopamine, theophylline, sodium bicarbonate, mannitol, fenoldopam, diuretics and nephrotoxic medicines within 48 h before a procedure	Patients with congestive heart failure, hypertension and diabetes mellitus, age above 75 years and renal insufficiency $< eGFR$ less than 60 ml/min/1.73 m <sup>2</sup> or baseline serum creatinine $> 1.5$ mg/dl	An increase in SCr levels by 44.2 $\mu$ mol/l (0.5 mg/dl) or 25% above the baseline within 24–48 h
Bodgah <i>et al.</i> /2019	The exclusion criteria were a history of acute/chronic renal failure, diabetes mellitus (DM), emergency angioplasty, and a family history of renal diseases	Patients aged $> 55$ years as well as with the first experience of angioplasty, elective procedures, and serum creatinine (SCr) value $> 1.1$ mg/kg were included in the study	An increase of $\geq 25\%$ in serum creatinine on 2 <sup>nd</sup> lab testing

### Data extraction and study characteristics

Screening was performed by two independent researchers (KM and MS). Eligible studies were included. Patients in all studies were subjected to either coronary angiography or percutaneous coronary intervention. The definition of contrast-induced nephropathy was generally the same across all RCTs with the exception of Erol *et al.* [4], who defined CIN as  $\geq 25\%$  elevation of serum cystatin C. Kumar in their study divided the study population into two groups based on the type of contrast medium used (Omnipaque and Visipaque); the same study had three arms (hydration alone, hydration with NAC and hydration with allopurinol). We used the groups as separate studies as different contrast media would likely confound the results if combined together [11]. Ghelich Khan *et al.* did not report the type of contrast medium used [12], while the rest of the studies utilized nonionic contrast media.

### Inclusion/exclusion criteria

Eligible randomized control trials, where comparison groups included patients pre-treated with allopurinol or a known treatment prior to undergoing cardiac catheterization (CA or PCI), were included. Measured outcomes were an increase of 0.5 mg/dl of serum creatinine (SCr), reduction of 25% from baseline eGFR, elevation of blood urea nitrogen (BUN), and elevation of uric acid (UA). Observational studies, pediatric studies and studies that did not report the abovementioned outcomes were excluded. The inclusion and exclusion criteria of the studies included in this meta-analysis are shown in Table I.

### Statistical analysis

We conducted a meta-analysis based on the random effects model according to DerSimonian and Laird methods using Comprehensive Meta-Analysis (CMA) Version 3.3.070. To compare the efficacy of treatment and placebo groups, we used odds ratios (OR) as a measure of effect. Heterogeneity in trials was assessed using the Q-statistic, which was quantified by  $I^2$  expressed as a percentage. It represents the non-random variation of the study, i.e., variation due to differences in study design, interventions, or populations. Heterogeneity was graded as follows:  $I^2 < 25\%$  = negligible,  $I^2 = 50\%$  = moderate and  $I^2 \geq 75\%$  = substantial. A funnel plot was used to assess publication bias.

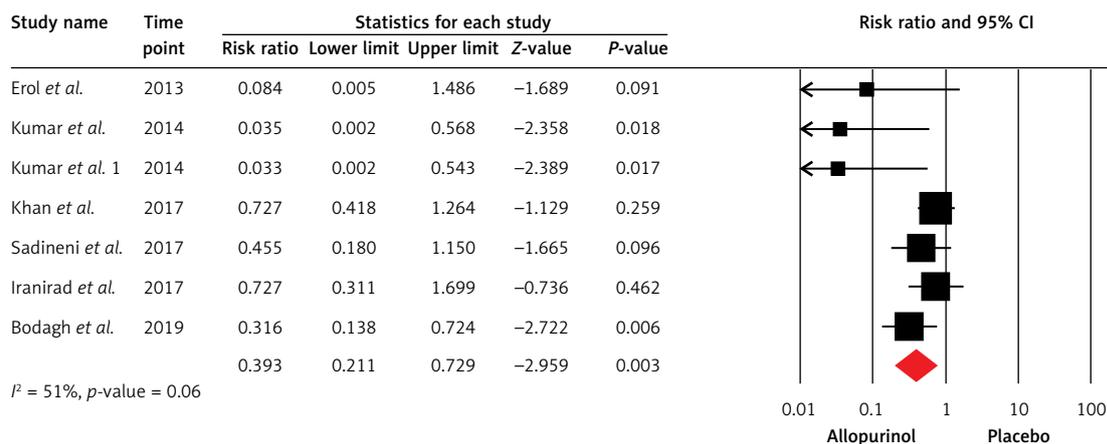
### Results

We retrieved 400 titles on our initial search. Based on pre-determined exclusion criteria, we excluded 376 articles. Out of the 24 articles left,

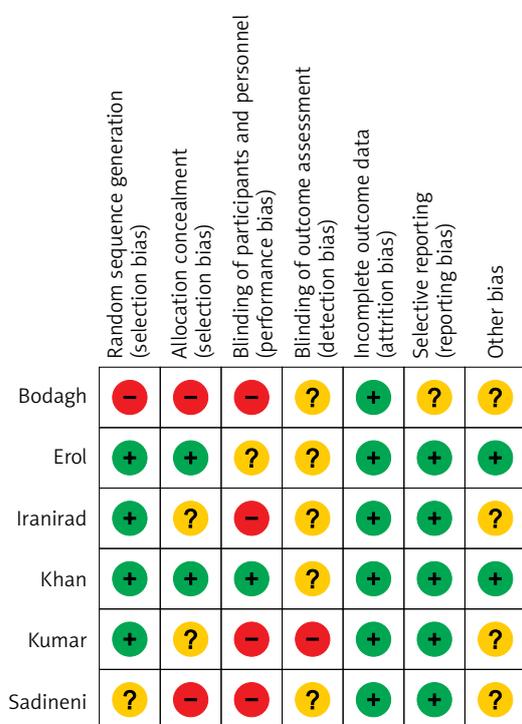
Table II. Baseline characteristics for all the studies included in our systematic review and meta-analysis

Authors/year	Design	N (C/Ctrl)	AKI (n/N)		ALL (SCr)	Ctrl (SCr)	Contrast administered in intervention and control group		NS* [ml/kg/h]	ALL [mg]	F/U [h]	Procedure	
			ALL	Ctrl			Contrast	ALL [ml]					Ctrl [ml]
Erol <i>et al.</i> /2013	RCT	159 (79/80)	0/79	6/80	1.43 [1.1-4.15]	1.48 [1.1-2.96]	Omnipaque	121 ±25	119 ±26	1	300	96	PCI and CA
Kumar <i>et al.</i> /2014	RCT	90 (45/45)	0/40	16/45	-	-	Omnipaque	-	-	1 <sup>+</sup>	300	120	PCI and CA
Kumar <i>et al.</i> /2014	RCT	95 (50/45)	0/50	15/50	-	-	Visipaque	-	-	1 <sup>+</sup>	300	120	PCI and CA
Ghelich <i>et al.</i> /2017	RCT	209 (101/108)	17/101	25/108	0.88 ±0.24	0.96 ±0.24	-	212.3 ±84.1	207.7 ±76.5	-	600	24	PCI
Sadini <i>et al.</i> /2017	RCT	60 (30/30)	5/30	11/30	1.91 ±0.72	2.19 ±1.01	Omnipaque	68.7 ±46.77	77.33 ±43.3	0.5 <sup>^</sup>	300	48	PCI and CA
Iranirad <i>et al.</i> /2017	RCT	140 (70/70)	8/70	11/70	1.2 ±0.3	1.1 ±0.3	Iodixanol	41.1 ±15.5	40.1 ±14.4	1	100	96	CA
Bodagh <i>et al.</i> /2019	RCT	100 (50/50)	6/50	19/50	-	-	-	-	-	-	300	72	PCI

C – cases, Ctrl – control, RCT – randomized controlled trial, SCr – serum creatinine, ALL – allopurinol, F/U – follow-up, NS – normal saline. \*12 h pre- and post-procedure, <sup>+</sup>ml/kg bw/min, <sup>^</sup>0.3 ml/kg/h for patients with ejection fraction < 40%.



**Figure 2.** Forest plot comparing efficacy of allopurinol and hydration with hydration alone in preventing CIN among patients undergoing percutaneous intervention



**Figure 3.** Risk of bias assessment for included studies

14 duplicates were removed, and 10 studies were considered eligible for full text review. Four studies were deemed unrelated to our study and six studies were included in the final analysis. Reasons of exclusion for the remainder of the studies are outlined in Figure 1. All included studies were clinical trials conducted between 2013 and 2019. A total of 853 evaluable patients were included and their baseline characteristics are shown in Table II.

They underwent either coronary angiography or percutaneous coronary intervention. The follow-up period was between 24 h and 5 days [4, 11–15]. Three out of the 7 clinical trials included patients with baseline SCr > 1.1–1.5 [4, 13, 14].

Included studies used Omnipaque or Visapique as the contrast agent. Most studies used 300 mg of allopurinol with hydration 24 h before administering contrast agent. Iranirad *et al.* used 100 mg of allopurinol and Ghelich *et al.* used 600 mg of allopurinol with hydration 24 h before intervention. There was a significant reduction in the risk of CIN among patients who were pretreated with adequate hydration plus allopurinol (100 to 600 mg) compared to hydration only before undergoing percutaneous coronary angiography (RR = 0.39, 95% CI: 0.21–0.73) (Figures 2, 3). A sensitivity analysis of studies using 300 mg of allopurinol only reported a significant reduction in CI-AKI compared to hydration alone (RR = 0.26, 95% CI: 0.11–0.57).

### Discussion

CIN is the third most common cause of hospital-acquired acute renal failure [16]. Diagnosis is usually based on a rise in serum creatinine after exposure to a contrast agent [16]. The pathophysiology of CIN is not fully understood. However, it is proposed that renal medullary hypoxia and direct tubular epithelial cell toxicity are the main factors responsible [17]. Contrast media cause intrarenal vasoconstriction with consequent reduction in renal perfusion, leading to ischemia, most pronounced in the renal medulla [17]. This effect is compounded by reactive oxygen species (ROS) produced by the polymorphonuclear cells attracted to the area of tissue damage [17]. Allopurinol is a substrate for xanthine oxidase and is oxidized to oxalopurinol, which is retained at the active site of the enzyme; the hydrogen-bonding potential of allopurinol makes it a potent inhibitor of xanthine oxidase [18]. An experimental study by Prieto-Moure *et al.* proved that allopurinol had a protective renal effect when used prior to or during renal ischemia in rats by decreasing lip-

id peroxidation and neutrophilic activation with a down regulatory effect in inflammatory cytokines [19]. Another human study demonstrated noteworthy variances in biochemical markers when allopurinol was compared to hydration for high risk patients, to prevent CIN, but no considerable effectiveness was found [13]. Another study demonstrated that allopurinol dosage of > 200 mg/day is independently protective against incident renal failure in elderly allopurinol users. The literature also reports that a longer duration of allopurinol use may be associated with lower risk of incident renal failure among allopurinol users [20]. It was reported that pre-procedural allopurinol significantly reduced the risk of CI-AKI (RR = 0.39, 95% CI: 0.20–0.74). It also led to a significant reduction in blood urea nitrogen levels (SMD = -0.40, 95% CI: -0.60 to -0.020) and a trend toward lower serum uric acid levels (SMD = -0.72,  $p = 0.01$ ). They did not report a dose-based sensitivity analysis which we performed, thereby supporting the core analysis as well as the findings of other meta-analyses. Our study was not without limitations. First, there was moderate heterogeneity in the results. It can be explained by baseline differences in kidney function of included patients. It is also a consequence of the two studies using a dose of 100 mg and 600 mg of allopurinol in contrast to a dose of 300 mg, which was predominantly used in many studies. Second, publication bias was observed in the funnel plot, which depicted under-reporting of studies that were not published because of insignificant results. Retrospectively, our findings are supported by a study that compared saline, acetylcysteine and allopurinol, which demonstrated significant results in the allopurinol + hydration arm compared to acetylcysteine and saline independently in patients undergoing percutaneous coronary angiography [11]. In summary, allopurinol showed a significant reduction in the rate of CI-AKI when compared to pre-procedural hydration alone. Sensitivity analysis of the 300 mg dose of allopurinol also reinforced the base case analysis. Further clinical trials may be warranted to establish guidelines when taking into account the absolute effectiveness of allopurinol in reducing rates of CI-AKI.

In conclusion, our study demonstrates that allopurinol has a protective effect in preventing contrast-induced nephropathy in patients undergoing percutaneous coronary intervention. Larger clinical trials are warranted to better understand this effect.

#### Conflict of interest

The authors declare no conflict of interest.

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