

# The role of pentoxifylline in preventing contrast-induced nephropathy in coronary angiography/intervention – systematic review, meta-analysis, and meta-regression of randomized controlled trials

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**Abstract.** – **OBJECTIVE:** This systematic review and meta-analysis aimed to synthesize the latest evidence on pentoxifylline effect on the contrast-induced nephropathy (CIN) and whether the quality evidence is sufficient to make a definite conclusion

**MATERIALS AND METHODS:** We performed a systematic literature search on topics that assesses pentoxifylline and CIN in coronary angiography/intervention up until 01 April 2021 using PubMed, Scopus, Embase, and hand-sampling. Primary outcome was CIN defined as  $\geq 0.5$  mg/dL or 25% rise in the SCr 48 h after procedure.

**RESULTS:** There were a total of 1142 subjects from 6 studies. There was no difference between pentoxifylline and control group in terms of serum creatinine at baseline ( $p=0.46$ ) and after the procedure ( $p=0.33$ ). The incidence of CIN was 51/571 (8.9%) in the pentoxifylline group and 61/571 (10.7%) in the control group. Pentoxifylline was not significantly associated with increase or decrease in the risk of CIN (RR 0.84 [0.59, 1.19],  $p=0.32$ ;  $I^2$ : 0%,  $p=0.89$ ). Subgroup analysis for elective studies showed a non-significant result (RR 0.77 [0.47, 1.27],  $p=0.31$ ;  $I^2$ : 0%). Meta-regression analysis showed that the association between pentoxifylline and mortality was not affected by age ( $p=0.994$ ), gender (reference: male,  $p=0.562$ ), hypertension ( $p=0.336$ ), diabetes ( $p=0.536$ ), baseline serum creatinine ( $p=0.344$ ), contrast used ( $p=0.431$ ), and CIN incidence ( $p=0.521$ ). GRADE Approach showed a low certainty of evidence for the effect estimate of pentoxifylline on CIN.

**CONCLUSIONS:** Our meta-analysis showed that pentoxifylline was not associated with the risk of CIN with low certainty of evidence. Hence, larger, multicentre, double-blind randomized controlled trials are required.

## Key Words:

Contrast-induced nephropathy, Coronary angiography, Meta-analysis, Pentoxifylline, Percutaneous coronary intervention.

## Introduction

Contrast-induced nephropathy (CIN) is defined as an increase in serum creatinine  $\geq 0.5$  mg/dL (44.2 mmol/L) or  $> 25\%$  of the baseline value 48-72 h after contrast media (CM) administration<sup>1</sup>. About 3 to 14% of the patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) experienced CIN and it is strongly associated with increased risk of mortality<sup>2-4</sup>. Various agents have been tested in an attempt to reduce the incidence of CIN, but most were disappointing and volume expansion through hydration remains the most integral component of the prophylaxis<sup>5</sup>.

Pentoxifylline is a methylxanthine derivative that is hypothesized to hold protective effect against CIN<sup>6</sup>. While a trial has shown the possibility of CIN reducing effect and recommending it<sup>7</sup>, subsequent investigations seemed to have denied the hypothesis. However, it is yet to be determined whether pentoxifylline is truly ineffective and further research should be abandoned, or whether the results of the trials have a poor quality of evidence resulting in a seemingly null effect. This systematic review and meta-analysis aimed to synthesize the latest evidence on pentoxifylline effect on the CIN and whether the quality evidence is sufficient to make a definite conclusion.

**Materials and Methods**

**Search Strategy**

We performed a systematic literature search on topics that assesses pentoxifylline and CIN in CAG/PCI patients with keywords (pentoxifylline) and (“contrast-induced nephropathy” or “contrast-induced acute kidney injury” or “contrast-induced renal injury”) from inception up until 01 April 2021 through PubMed, SCOPUS, Embase, and hand-sampling from potential articles cited by other studies. The records were then systematically evaluated using inclusion and exclusion criteria. We also performed hand-sampling from references of the included studies. Two researchers independently performed an initial search and discrepancies were resolved by discussion. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the literature search strategy of studies was presented in Figure 1.

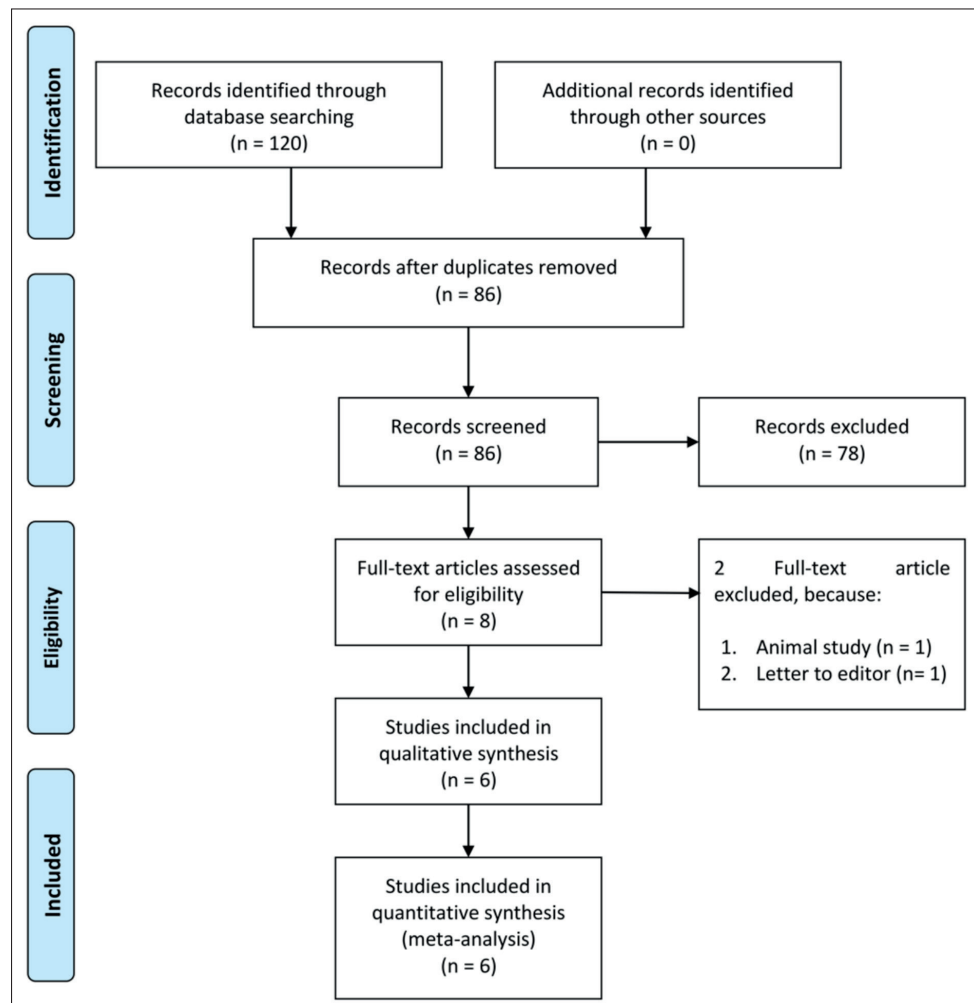
**Selection Criteria**

The inclusion criteria for this study are all studies that assess pentoxifylline and CIN in patients undergoing CAG and/or PCI. We include randomized controlled trials (RCT) and exclude case reports, review articles, and non-English language articles.

**Data Extraction**

Data extraction and quality assessment were done by two independent authors using standardized extraction form which includes authors, year of publication, study design, subject characteristics, CAG/PCI procedure, sample size, pentoxifylline protocol details, components of CIN prevention, male, age, CIN definition, CIN incidence, major adverse events, and funding of each study.

Primary outcome was CIN defined as  $\geq 0.5$  mg/dL or 25% rise in the SCr 48 h after CM exposure and the secondary outcome was serum creatinine at baseline and after the procedure.



**Figure 1.** Study flow diagram.

### Statistical Analysis

To perform the meta-analysis, we used RevMan version 5.4 software (Cochrane Collaboration) and STATA 16.0 (StataCorp LP). We used the relative risk (RR) and a 95% CI as a pooled measure for dichotomous data. We used mean difference (MD) and its standard deviation (SD) as a pooled measure for the continuous data. Inconsistency index ( $I^2$ ) test, which ranges from 0 to 100%, was used to assess heterogeneity across studies. A value  $>50\%$  or  $p < 0.10$  indicates statistically significant heterogeneity. We used the Mantel-Haenszel method for RR and the Inverse Variance method for mean difference, with a fixed-effect model for meta-analysis, and a random-effect model was used in case of heterogeneity. The small-study effect was assessed using a regression-based test (Egger's test) for binary outcomes. All  $p$ -values were two-tailed with a statistical significance set at 0.05 or below. The certainty of the evidence was assessed by using the Guideline Development Tool by GRADEpro GDT. Random-effects restricted likelihood meta-regression analysis was performed using age, gender, hypertension, diabetes, baseline serum creatinine, contrast media use, and CIN incidence as covariates.

## Results

### Study Selection and Characteristics

We found a total of 120 results. There were 86 records after the removal of duplicates 78 records were excluded after screening the title/abstracts. After assessing 8 full-text for eligibility; we excluded 2 because 1) animal study ( $n = 1$ ), 2) letter to editor ( $n = 1$ ). We included 6 studies<sup>7-12</sup> in qualitative synthesis and meta-analysis (Figure 1). All 6 studies were RCTs. There were a total of 1142 subjects from 6 studies<sup>7-12</sup> (Table I and Table II).

There were 4 studies<sup>7-9,11</sup> that enrolled patients undergoing elective procedure and 2 in those undergoing primary PCI<sup>10,12</sup>. The definition for CIN was mostly  $\geq 0.5$  mg/dL or 25% in the SCr 48 h after CM exposure. There is one study that also included Cystatin C. Only one study<sup>9</sup> was a double-blind, placebo-controlled RCT. There are 2 studies<sup>8-9</sup> that provide n-acetylcysteine as a mode of preventing CIN in both intervention and control groups.

### Serum Creatinine

There was no difference between pentoxifylline and control group in terms of serum creatinine at baseline (mean difference 0.02 [-0.04, 0.08],  $p=0.46$ ;  $I^2: 0\%$ ,  $p=0.72$ ) (Figure 2A) and after the procedure (mean difference 0.04 [-0.04, 0.11],  $p=0.33$ ;  $I^2: 0\%$ ,  $p=0.62$ ) (Figure 2B).

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### Contrast-Induced Nephropathy

The incidence of CIN was 51/571 (8.9%) in the pentoxifylline group and 61/571 (10.7%) in the control group. Pentoxifylline was not significantly associated with increase or decrease in the risk of CIN (RR 0.84 [0.59, 1.19],  $p=0.32$ ;  $I^2: 0\%$ ,  $p=0.89$ ) (Figure 2C).

### Subgroup Analysis

Subgroup analysis for elective studies showed a non-significant result (RR 0.77 [0.47, 1.27],  $p=0.31$ ;  $I^2: 0\%$ ,  $p=0.79$ ).

### Meta-Regression

Meta-regression analysis showed that the association between pentoxifylline and CIN was not affected by age ( $p=0.994$ ) (Figure 3A) gender (reference: male,  $p=0.562$ ), hypertension ( $p=0.336$ ), diabetes ( $p=0.536$ ), baseline serum creatinine ( $p=0.344$ ) (Figure 3B), contrast used ( $p=0.431$ ) (Figure 3C), and CIN incidence ( $p=0.521$ ).

### Risk of Publication Bias

The risk of publication bias was due to inadequate blinding, several unclear allocation concealments, and lack of placebo (Figure 4A). Funnel-plot analysis was relatively asymmetrical (Figure 4B). Non-parametric trim-and-fill analysis by imputation of two studies in the left side of the plot showed RR of 0.77 [0.55, 1.06] (Figure 4C). Regression-based Egger's test was not significant for small-study effects ( $p=0.468$ ).

### GRADE Approach

GRADE Approach showed a low certainty of evidence for the effect estimate of pentoxifylline on CIN (Table III). This was due to the serious risk of bias and imprecision. Confidence intervals included potential for important benefit with the risk ratio  $<0.75$  but not  $>1.25$ .

## Discussion

Our meta-analysis showed that pentoxifylline was not associated with the risk of CIN with low certainty of evidence. The interpretation is limited due to the low certainty of evidence. Serious

**Table I.** Studies included in the systematic review.

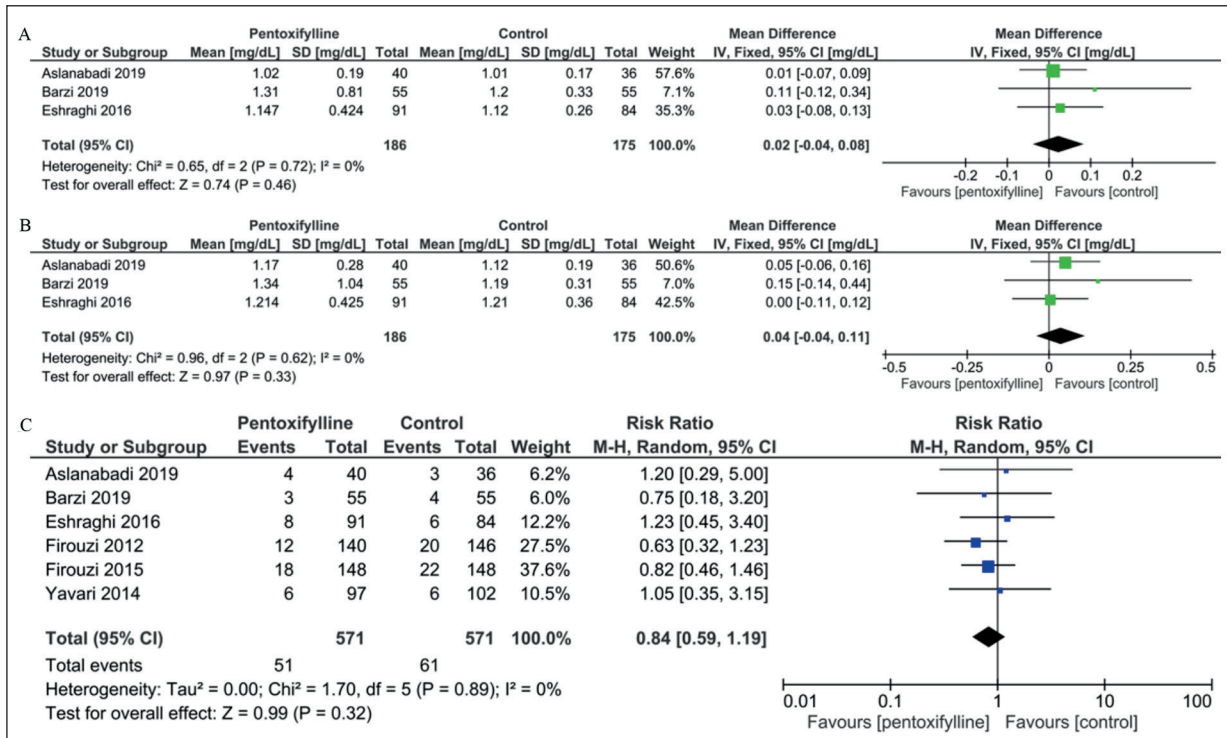
First author	Study design	Inclusion criteria	Definition of CIN	PTX protocol	Control group	CIN prevention protocol	Sample size	Funding
Aslanabadi et al <sup>8</sup> 2019	RCT	Coronary Angioplasty Diabetic patients	≥ 0.5 mg/dL or 25% rise in the Cystatin C or SCr 24 h after CM exposure	400 mg 3×/daily from 2-4 hours before CM exposure	None	Normal Saline + NAC 600 mg 2×/daily before and after procedure + bicarbonate	40/36	Cardiovascular Research Center of Shahid Madani, Tabriz University of Medical Sciences
Barzi et al <sup>9</sup> 2019	Double-blind RCT	CAG with Mehran score ≥ 11	≥ 0.5 mg/dL in the SCr 48 h after CM exposure	400 mg 3×/daily from 24 hours before to 48 hours after CM exposure + NAC	Placebo	Normal Saline + NAC 1200 mg 2×/daily from 24 hours before to 48 hours after	55/55	Shahid Beheshti University of Medical Sciences and Amin Pharmaceutical Co
Eshraghi et al <sup>10</sup> 2016	RCT	Primary PCI in STEMI	≥ 0.5 mg/dL or 25% rise in the SCr 48 h after CM exposure	400 mg 3×/daily until 24 after CM exposure	None	Normal Saline	91/84	Unclear
Firouzi et al <sup>7</sup> 2012	RCT	Non-emergent CAG/Intervention	≥ 0.5 mg/dL or 25% rise in the SCr 48 h after CM exposure	400 mg 3×/daily from 24 hours before to 24 hours after CM exposure	None	Normal Saline	140/146	Unclear
Firouzi et al <sup>12</sup> 2015	RCT	Primary PCI in STEMI	≥ 0.5 mg/dL or 25% rise in the SCr 48 h after CM exposure	400 mg 3×/daily until 24 hours after CM exposure	None	Normal Saline	148/148	
Yavari et al <sup>11</sup> 2014	RCT	Elective PCI	25% rise in the SCr 48 h after CM exposure	400 mg 3×/daily from the day of procedure to 24 hours after CM exposure	None	Normal Saline	97/102	Vice-Chancellery of Research and Technology and Shiraz Nephro- urology Research Center, Shiraz University of Medical Sciences

**Table II.** Characteristics of the patients included in the systematic review.

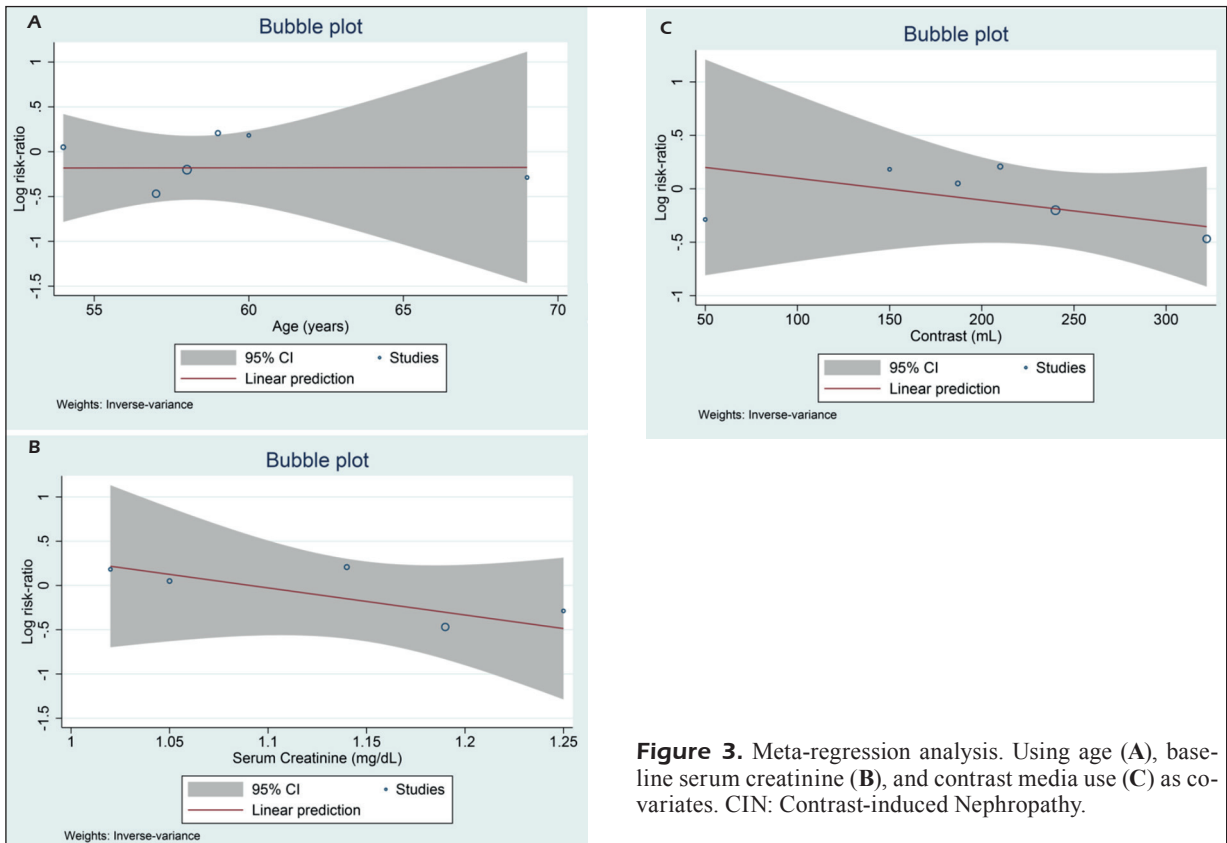
First Author	Age (mean $\pm$ SD)	Male (%)	Hypertension (%)	Diabetes (%)	Creatinine	Contrast (mL)	CIN Incidence (%)
Aslanabadi et al <sup>8</sup> 2019	62.9 $\pm$ 10.0 vs. 58.3 $\pm$ 7.3	35.5 vs. 51.1	67.5 vs. 63.9	100 vs. 100	1.02 vs. 1.01	150 vs. 150	10.0 vs. 8.3
Barzi et al <sup>9</sup> 2019	70.10 $\pm$ 11.80 vs. 68.30 $\pm$ 10.83	41.8 vs. 52.7	72.7 vs. 61.8	52.7 vs. 61.8	1.31 vs. 1.20	50	5.5 vs. 7.3
Eshraghi et al <sup>10</sup> 2016	60.46 $\pm$ 14.03 vs. 57.90 $\pm$ 14.27	67 vs. 79	52 vs. 32	45 vs. 35	1.15 vs. 1.12	190.9 vs. 231.3	8.8 vs. 7.1
Firouzi et al <sup>7</sup> 2012	56.8 $\pm$ 10.69 vs. 57.9 $\pm$ 10.16	76.4 vs. 69.17	35 vs. 46.5	20.7 vs. 32.19	1.17 vs. 1.21	319.3 vs. 325.3	8.6 vs. 13.7
Firouzi et al <sup>12</sup> 2015	58.4 vs. 58.2	79.1 vs. 80.4	43.9 vs. 45.9	33.1 vs. 33.1	NA	240 vs. 240	12.2 vs. 14.9
Yavari et al <sup>11</sup> 2014	54.44 $\pm$ 7.61 vs. 53.72 $\pm$ 7.71	N/A	41.2 vs. 48	27.8 vs. 22.5	1.06 vs. 1.04	192.0 vs. 185.9	6.2 vs. 5.9

Description = CIN: Contrast-induced Nephropathy; CM: Contrast Media; NAC: N-acetylcysteine; PTX: Pentoxifylline; RCT: Randomized Controlled Trial; SCr: Serum Creatinine; SD: Standard Deviation.

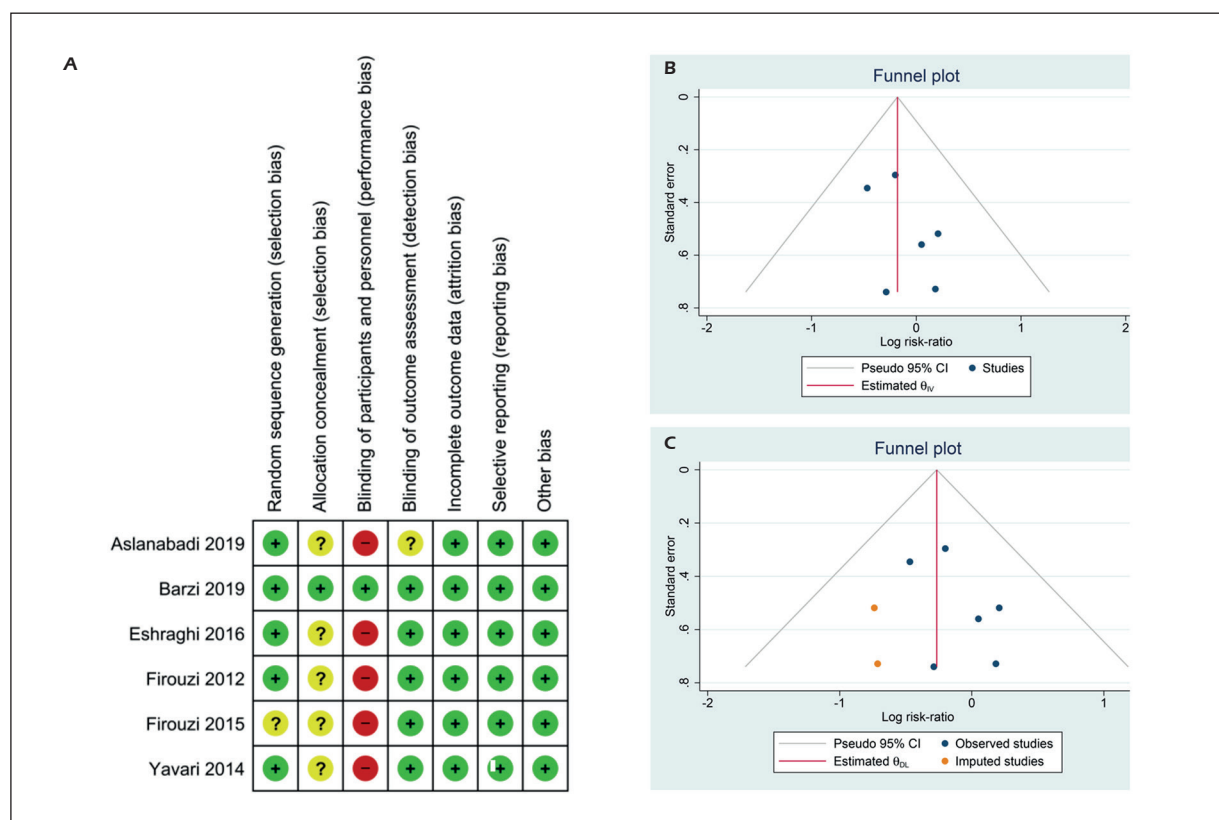
## Pentoxifylline and CIN



**Figure 2.** Renal Function. **A, B,** Showing no difference in terms of serum creatinine at baseline and after the procedure in pentoxifylline and control group, respectively. **C,** Showing that pentoxifylline was not associated with the risk of CIN. CIN: Contrast-induced Nephropathy.



**Figure 3.** Meta-regression analysis. Using age (**A**), baseline serum creatinine (**B**), and contrast media use (**C**) as covariates. CIN: Contrast-induced Nephropathy.



**Figure 4.** Publication Bias. **A**, Risk assessment using Cochrane risk-of-bias tool for randomized trials. **B**, Asymmetrical funnel-plot. **C**, Non-parametric trim-and-fill analysis by imputation of two studies in the left side of the plot. CIN: Contrast-induced Nephropathy.

imprecision may cause the study to seemingly have a null effect, but a sizeable swing in RR from 1 may indicate an effect that is not yet observable. Firouzi et al<sup>7</sup> study, which has the largest sample size and the highest incidence of CIN, showed a lower incidence of CIN in pentoxifylline group, albeit not statistically significant. The studies included also have a wide range of confidence intervals. These factors may indicate that the sample size was inadequate to detect observable change. However, it should be noted that the study conducted by Firouzi et al<sup>7</sup>, showed a significantly higher prevalence of diabetes (32.2% vs. 20.7%,  $p=0.02$ ) and hypertension (35% vs. 46.5%,  $p=0.047$ ) in the control group compared to the pentoxifylline group that may confound the study results. Eshraghi et al<sup>10</sup> reported a higher prevalence of hypertension in pentoxifylline but a higher contrast used in the control group which may confound the outcome measurement.

The trials seemed to be underpowered to make statistical conclusions close to the true effect and

some studies did not have similar baseline characteristics between the intervention and control group. The number of events was also insufficient to perform multivariate analysis without overfitting the model. Additionally, using the non-parametric trim-and-fill analysis indicates that the confidence interval of the effect estimate moved to the left. These indicate that a definite conclusion cannot be drawn, as a larger (preferably multicentre), double-blind RCTs to make sure whether the effect was truly null or due to small event rates. Further pentoxifylline studies are justified based on the lack of other preventive therapies beyond parenteral hydration. The authors recommend that the use of pentoxifylline to reduce CIN be limited for clinical trials and should be avoided in routine clinical practice.

Pentoxifylline is a methylxanthine derivative with multiple haematologic properties, it has an anti-inflammatory effect, reduces nitric oxide destruction, improves oxygen delivery, and reduces free radicals<sup>6,13,14</sup>. The complete picture of CIN pathophysiology remained elusive; how-

Pentoxifylline and CIN

**Table III.** GRADE approach.

Certainty assessment							No. of patients		Effect		Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PTX	Control	Relative (95% CI)	Absolute (95% CI)	
<b>Contrast-induced nephropathy</b>											
6	Randomised trials	Serious <sup>a</sup>	Not serious	Not serious	Serious <sup>b</sup>	None	51/571 (8.9%)	61/571	RR 0.84 (0.59 to 1.19)	17 fewer per 1,000 (from 44 fewer to 20 more)	⊗⊗○○ LOW

CI: Confidence interval; RR: Risk ratio. Explanations: <sup>a</sup>Inadequate blinding, several unclear allocation concealments, lack of placebo. <sup>b</sup>Confidence intervals included potential for important harm or benefit (and seemingly null effect), the risk ratio < 0.75.

ever, reduction of nitric oxide production, vasoconstriction, renal ischemia, ischemia/reperfusion injury, and reactive oxygen species are among the causes<sup>15,16</sup>. Interventions that alleviate ischemia/reperfusion injury and oxidative stress have been shown to reduce CIN incidence<sup>17,18</sup>. The pharmacology of pentoxifylline seemed to counteract the abovementioned mechanisms involved in the pathophysiology of CIN. Indeed, pentoxifylline has been shown to be protective for renal ischemia-reperfusion injury in animal models<sup>19</sup>; however, there is currently a lack of animal study investigating pentoxifylline and CIN.

Other limitations of this systematic review and meta-analysis were the limited number of studies and events, the sample size seemed to be underpowered for such analysis. All the studies are also from Iran and the results cannot be generalized to other populations. Trials abroad may offer different perspectives and results. In addition to larger sample size, the trials can also investigate the efficacy of pentoxifylline in patients with moderate to high risk of CIN defined as estimated glomerular filtration rate (eGFR)  $\leq 60$  ml/min/1.73 m<sup>2</sup>. Trials should also assess major adverse cardiovascular events and mortality in addition to the incidence of CIN.

## Conclusions

Our meta-analysis showed that pentoxifylline was not associated with the risk of CIN with low certainty of evidence. Hence, larger, multicentre, double-blind RCTs are required before drawing a definite conclusion.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Ethics Approval and Consent to Participate

Not applicable due to nature of systematic review and meta-analysis which did not include primary data from patients, but only data reported by published studies.

### Authors' Contribution

Januar Wibawa Martha: conceptualization, investigation, writing – review and editing, supervision. Raymond Pranata: conceptualization, methodology, software, data curation, formal analysis, investigation, validation, writing – original draft, writing – review and editing. Wilson Mat-

thew Raffaello: data curation, investigation, writing – original draft Arief Wibowo: investigation, writing – original draft Mohammad Rizki Akbar: investigation, writing – review and editing.

## References

- 1) van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, Clement O, Heinz-Peer G, Stacul F, Webb JAW, Thomsen HS. Post-contrast acute kidney injury – Part 1: Definition, clinical features, incidence, role of contrast medium and risk factors: Recommendations for updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol* 2018; 28: 2845-2855.
- 2) McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: Incidence, risk factors, and relationship to mortality. *Am J Med* 1997; 103: 368-375.
- 3) Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002; 105: 2259-2264.
- 4) Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, Kosiborod M, Amin AP, Messenger JC, Rumsfeld JS, Spertus JA. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: Insights from the NCDR cath-PCI registry. *JACC Cardiovasc Interv* 2014; 7: 1-9.
- 5) Weisbord SD, Palevsky PM. Prevention of contrast-induced nephropathy with volume expansion. *Clin J Am Soc Nephrol* 2008; 3: 273-280.
- 6) Roozbeh J, Jahromi AH, Sharifian M, Pakfetrat M, Afshariani R. Protective effect of pentoxifylline on contrast induced nephropathy. *Saudi J Kidney Dis Transpl* 2008; 19: 985-986.
- 7) Firouzi A, Eshraghi A, Shakerian F, Sanati HR, Salehi N, Zahedmehr A, Kiani R, Maani M, Pedarzadeh A. Efficacy of pentoxifylline in prevention of contrast-induced nephropathy in angioplasty patients. *Int Urol Nephrol* 2012; 44: 1145-1149.
- 8) Aslanabadi N, Afsar Gharebagh R, Moharramzadeh S, Entezari-Maleki T. Pentoxifylline for the prevention of contrast-induced nephropathy in diabetic patients undergoing angioplasty: a randomized controlled trial. *Int Urol Nephrol* 2019; 51: 699-705.
- 9) Barzi F, Miri R, Sadeghi R, Sistanizad M, Sadeghi M, Mahjoob MP, Chehrazhi M. A randomized double blind placebo controlled trial examining the effects of pentoxifylline on contrast induced nephropathy reduction after percutaneous coronary intervention in high risk candidates. *Iran J Pharm Res* 2019; 18: 1040-1046.

- 10) Eshraghi A, Naranji-Sani R, Pourzand H, Vojdanparast M, Morovatfar N, Ramezani J, Khamene-Bagheri R, Nezafati P. Pentoxifylline and prevention of contrast-induced nephropathy: Is it efficient in patients with myocardial infarction undergoing coronary angioplasty? *ARYA Atheroscler* 2016; 12: 1-5.
- 11) Yavari V, Ostovan MA, Kojuri J, Afshariani R, Hamidian A, Roozbeh J, Pakfetrat M. The preventive effect of pentoxifylline on contrast-induced nephropathy: A randomized clinical trial. *Int Urol Nephrol* 2014; 46: 41-46.
- 12) Firouzi A, Shahsavari H, Kiani R, Aeinfar K, Shamloo Y, Mortezaian H. Evaluation of Pentoxifylline in the Prevention of Contrast-Induced Nephropathy in Patients Undergoing Primary Percutaneous Coronary Intervention. *Iran Hear J* 2015; 16: 28-34.
- 13) Stafford-Smith M. Evidence-based renal protection in cardiac surgery. *Semin Cardiothorac Vasc Anesth* 2005; 9: 65-76.
- 14) Dávila-Esqueda ME, Martínez-Morales F. Pentoxifylline diminishes the oxidative damage to renal tissue induced by streptozotocin in the rat. *Exp Diabetes Res* 2004; 5: 245-251.
- 15) Rear R, Bell RM, Hausenloy DJ. Contrast-induced nephropathy following angiography and cardiac interventions. *Heart* 2016; 102: 638-648.
- 16) Yang JS, Peng YR, Tsai SC, Tyan YS, Lu CC, Chiu HY, Chiu YJ, Kuo SC, Tsai YF, Lin PC, Tsai FJ. The molecular mechanism of contrast-induced nephropathy (CIN) and its link to in vitro studies on iodinated contrast media (CM). *Biomed* 2018; 8: 1-11.
- 17) Pranata R, Vania R, Alkatiri AA, Firman D, Lukito AA. Nicorandil Reduces the Incidence of Contrast-Induced Nephropathy in Patients Undergoing Coronary Angiography/Intervention – Systematic Review and Meta-Analysis of Randomized Controlled Trials Including GRADE Qualification. *Cardiovasc Revascularization Med* 2020; 21: 1121-1127.
- 18) Pranata R, Tondas AE, Vania R, Toruan MPL, Lukito AA, Siswanto BB. Remote ischemic preconditioning reduces the incidence of contrast-induced nephropathy in patients undergoing coronary angiography/intervention: Systematic review and meta-analysis of randomized controlled trials. *Catheter Cardiovasc Interv* 2020; 96: 1200-1212.
- 19) Wystrychowski W, Wystrychowski G, Zukowska-Szzechowska E, Obuchowicz E, Grzeszczak W, Więcek A, Wystrychowski A. Nephroprotective effect of pentoxifylline in renal ischemia-reperfusion in rat depends on the timing of its administration. *Transplant Proc* 2014; 46: 2555-2557.