European Review for Medical and Pharmacological Sciences 2021; 25: 3045-3053

The effect of trimetazidine on contrast-induced nephropathy in patients undergoing coronary angiography and/or percutaneous coronary intervention – A systematic review and meta-analysis

J.W. MARTHA[1], R. PRANATA[2], A. WIBOWO[1], I. IRVAN[2], R. AFRIANTI[1], M.R. AKBAR[1]

[1]Department of Cardiology and Vascular Medicine, Faculty of Medicine Universitas Padjadjaran, Rumah Sakit Umum Pusat Hasan Sadikin, Bandung, Indonesia
[2]Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

Abstract. – OBJECTIVE: In this study, we aimed to evaluate whether the trimetazidine administration before CAG and/or PCI reduces the incidence of contrast-induced nephropathy (CIN). We also aimed to evaluate the factors affecting the effect and the certainty of the evidence.

MATERIALS AND METHODS: A systematic literature search was performed to obtain studies that assess trimetazidine's effect on the incidence of CIN in CAG/PCI patients up until 21 January 2021 through PubMed, Embase, and Scopus. The main outcome is CIN, defined as the increase in serum creatinine level ≥ 0.5 mg/dL (44.2 mmol/L) or > 25% of the baseline value 48-72 h after contrast media (CM) administration.

RESULTS: This systematic review and meta-analysis includes seven studies involving a total of 1590 patients. The prevalence of CIN was 11% [8%, 14%]. CIN's prevalence was 6% [4%, 8%] in the trimetazidine group and 16% [12%, 20%] in the control group. Trimetazidine use is associated with a lower incidence of CIN (RR 0.46 [0.34, 0.63], $p<0.001$; I^2: 0%) with a high certainty of evidence, with an absolute risk reduction of 78 fewer per 1000. Subgroup analysis in patients with renal insufficiency showed that trimetazidine lowers the risk of CIN (RR 0.40 [0.26, 0.61], $p<0.001$; I^2: 0%). The CIN reducing effect of trimetazidine was not significantly influenced by the age ($p=0.960$), body mass index ($p=0.816$), hypertension ($p=0.595$), diabetes ($p=0.362$), ejection fraction ($p=0.261$), baseline serum creatinine (0.579), and contrast media volume ($p=0.958$).

CONCLUSIONS: Trimetazidine administration decreases the risk of CIN in patients undergoing CAG/PCI.

Key Words:
Angiography, Cardiovascular, Contrast-induced acute kidney injury, Contrast media, Renal insufficiency.

Introduction

Contrast-induced nephropathy (CIN) is a condition in which there is a worsening of renal function after administering contrast media. It occurs in 3% to 14% after coronary angiography (CAG) or percutaneous coronary intervention (PCI) procedure, and more frequently in patients with renal dysfunction[1-3]. CIN is associated with mortality following CAG/PCI[4]. Adequate hydration remained pivotal in CIN prevention. Although there are several interventions proposed to reduce CIN, most results are inadequate or equivocal[5].

Trimetazidine is an anti-ischemic drug that inhibits the long-chain mitochondrial 3-ketoacyl coenzyme A thiolase enzyme, improving the mitochondrial metabolism[6]. By inhibiting free fatty acids oxidation, metabolism in cardiac and muscle shifts to glucose utilization[7]. Pyruvate dehydrogenase activity is enhanced by trimetazidine; it restores homeostasis between glucose oxidation and glycolysis, which are disrupted due to ischemia[8,9]. Thus, trimetazidine decrease oxygen consumption, intracellular calcium ion, and intracellular acidity[9,10]. Attenuating the energy insufficiency results in decreased reactive oxygen species (ROS) formation[11]. These mechanisms

Corresponding Author: Januar Wibawa Martha, MD, MPH, Ph.D; e-mail: jwmartha@gmail.com

promote membrane stabilization of the cells[12]. Trimetazidine may protect against free radical damage due to its antioxidant activity, thus may attenuate renal ischemic-reperfusion injury[13,14]we evaluated the effect of trimetazidine (TMZ. In this study, we aimed to evaluate whether the trimetazidine administration before CAG and/or PCI reduces the incidence of CIN. We also aimed to evaluate the factors affecting the effect and the certainty of the evidence.

Materials and Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline (Figure 1).

Eligibility Criteria

The inclusion criteria include: (1) Randomized controlled trials assessing trimetazidine compared to control in patients undergoing CAG and/or PCI, (2) Reporting the incidence of CIN.

The exclusion criteria were: (1) conference abstracts, (2) case reports, (3) review articles, (4) preprints, and (5) non-English language articles.

Intervention and Outcome

The intervention was trimetazidine administered before CAG and/or PCI. The control was standard of care.

The main outcome is CIN, defined as the increase in serum creatinine level ≥ 0.5 mg/dL (44.2 mmol/L) or > 25% of the baseline value 48-72 h after contrast media (CM) administration[15]. The effect estimate was reported as risk ratio (RR) along with its 95% confidence interval (95% CI).

Search Strategy

A systematic literature search was performed to obtain studies that assess the effect of trimetazidine on the incidence of CIN in

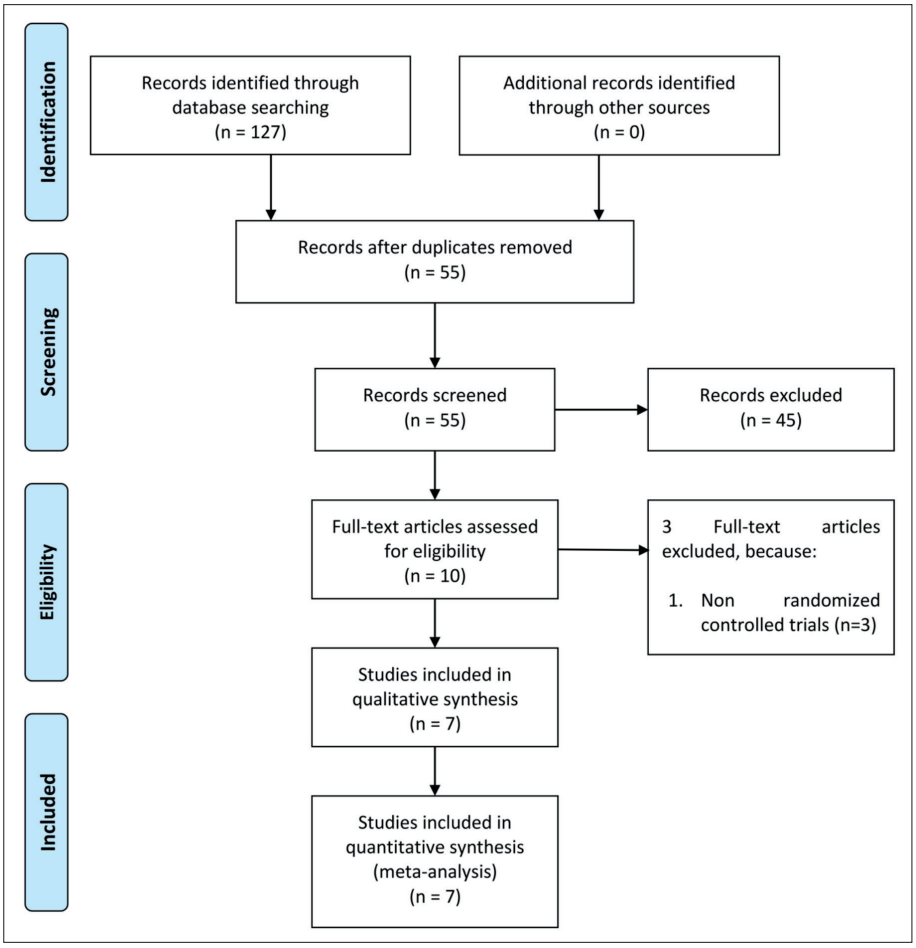

Figure 1. PRISMA flowchart.

CAG/PCI patients with keywords ["trimetazidine" and "contrast-induced nephropathy" OR "contrast-induced acute kidney injury" OR "contrast-induced acute renal injury"] and its synonym from inception up until 21 January 2021 through PubMed, Embase, and Scopus. According to the inclusion and exclusion criteria, two independent authors performed a literature search and articles' eligibility assessment. Discrepancies were resolved by discussion.

Data Extraction

Two authors independently performed data extraction for several variables, including first author, year of publication, study design, sample size, baseline characteristics of the patients, trimetazidine protocol details, definition of CIN, and CIN incidence.

Assessment of Methodology Criteria and Risk of Bias

Cochrane Risk of Bias Assessment Tool was used to facilitate the assessment of the included studies. This was performed by two authors independently, and discrepancies were resolved by discussion. Guideline Development Tool by GRADEpro GDT was used to evaluate the certainty of evidence.

Statistical Analysis

STATA 16.0 (StataCorp LP) was used to perform a meta-analysis. Random-effects meta-analysis of proportion was performed to pool the incidence of CIN. We calculated the RRs and their 95% CI by pooling dichotomous data using the DerSimonian-Laird method random-effects model. A p-value <0.05 for the effect estimate was considered statistically significant. The inconsistency index (I^2) test and Cochran Q test were used to evaluate heterogeneity across the studies. An I^2-test value above 50% and/or p-value <0.10 indicates substantial heterogeneity.

Assessment of Publication Bias

We performed funnel-plot analysis and Egger's test to evaluate the possibility for small-study effects, qualitative and quantitatively. Trim-and-fill analysis (Linear 0 estimator) was performed due to asymmetrical funnel-plot.

Exploration of Heterogeneity

Meta-regression analysis was performed to evaluate the association between trimetazidine and CIN using several characteristics and confounders as covariates. Subgroup analysis was performed for patients with renal insufficiency.

Results

Baseline Characteristics

This systematic review and meta-analysis includes seven studies involving a total of 1590 patients[16-22]. The baseline characteristic of these studies is displayed in Table I. The prevalence of CIN was 11% [8%, 14%].

Contrast-Induced Nephropathy

The incidence of CIN was 6% [4%, 8%] in trimetazidine group and 16% [12%, 20%] in the control group. Trimetazidine use is associated with lower incidence of CIN (RR 0.46 [0.34, 0.63], p<0.001; I^2: 0%, (p=0.888) (Figure 2). Subgroup analysis in patients with renal insufficiency showed that trimetazidine lowers the risk of CIN (RR 0.40 [0.26, 0.61], p<0.001; I^2: 0%, (p=0.930).

Meta-Regression

The CIN reducing effect of trimetazidine was not significantly influenced by the age ((p=0.960), body mass index ((p=0.816), hypertension (p=0.595), diabetes ((p=0.362), ejection fraction ((p=0.261), baseline serum creatinine (0.579), and contrast media volume ((p=0.958).

Risk of Bias Assessment

The Cochrane Risk of Bias Assessment is displayed in (Figure 3). Funnel-plot was asymmetrical (Figure 4) and the Trim-and-fill analysis (Linear 0 estimator) showed that the imputation of 3 studies on the right side of the plot resulted in RR of 0.50 [0.38, 0.67] (Figure 5). Egger's test showed no indication of small-study effects in this pooled analysis ((p=0.172).

GRADE Assessment

GRADE assessment showed a high certainty of evidence for the effect of trimetazidine on CIN reduction with an absolute risk reduction of 78 fewer per 1000 (Table II).

Discussion

This meta-analysis indicates that trimetazidine administration decreases CIN's risk in patients undergoing CAG/PCI, especially in patients with

Table I. Studies included in the systematic review.

Author	Study design	Subject characteristics	Procedure	CIN Definition	Sample size (n)	Male (%)	Age (mean age in years)	BMI (kg/m²)	HT (%)	DM (%)	Dyslipidemia (%)	LVEF (%)	SCr (mg/dL)	CrCl (ml/min)	eGFR (mL/min 1.73 m²)	Contrast amount (mL)	Funding
Fu 2020	RCT	CrCl < 60ml/min	PCI	SCr elevation > 25% from baseline or > 0.5 mg/dl absolute at 48 to 72 hours	310	49.4%	76.8 ± 4.4	22.6 ± 2.5	57	45.5	NA	(LVEF < 45%) 7.7%	1.14 ± 0.17	NA	73.9 ± 13.5	141.7 ± 16.7	None
Liu 2015	RCT	eGFR 30 to	CAG/PCI < 90 ml/min/ 1.73 m² LVEF > 35	SCr elevation > 25% from baseline or > 0.5 mg/dl absolute at 48 to 72 hours	132	56.8	58.6 ± 10.9	26.3 ± 2.4	54.5	60.6	25.8	NA	1.19 ± 0.25	NA	NA	122.15 ± 33.05	NA
Mirhosseni 2019	RCT	eGFR 30-60 mL/	CAG min/1.73 m² LVEF > 45% with no urgent indication for angiography	SCr elevation > 25% from baseline or > 0.5 mg/dl absolute at 48 to 72 hours	100	44	66 ± 4.33	66 ± 5.96	62	63	NA	51 ± 4.504	1.28 ± 0.14	NA	50 ± 7.47	119.3	NA
Onbasili 2007	Double-blinded,	SCr ≥1.2 mg/d CrCl < 50ml/min	CAG/PCI	SCr elevation >25% from baseline or >0.5 mg/dl absolute at 24 to 48 hours	82	69	60.5 ± 10.5	26.2 ± 3.5	NA	23.2	NA	47.48 ± 18.89	1.28 ± 0.209	53.37 ± 11.98	NA	233.5	NA
Shehata 2014	RCT	eGFR 30 to < 90 ml/min/1.73 m²	PCI	SCr elevation > 25% from baseline or > 0.5 mg/dl absolute at 72 hours.	100	68	58.5 ± 5.5	27.5 ± 3.0	48	100	30	54.5 ± 7.49	2 ± 0.45	NA	48.5 ± 15.50	275 ± 13.64	NA
Ye 2017	RCT	Diabetes and renal insufficiency eGFR 30-89 mL/ min/1.73 m2	CAG/PCI	SCr elevation > 25% from baseline or > 0.5 mg/dl absolute at 48 to 72 hours	106	59	64.2 ± 8.5	NA	70	100	53.8	NA	NA	NA	NA	NA	None
Zhang 2020	RCT, Multi-center trial	Patients ≥ 60 yrs. Patients with diabetes LVEF > 30%	PCI	SCr elevation >25% from baseline or > 0.5 mg/dl absolute at 48 to 72 hours	760	69	67 ± 6.6	24.9 ± 2.3	41.0	NA	NA	59.42 ± 8.271	0.92 ± 0.28	72.10 ± 13.05	NA	170.3 ± 67.0	Tianjin Municipal Health and Family Planning Commission

RCT, Randomized Controlled Trial; BMI, Body Mass Index; LVEF, Left Ventricular Ejection Fraction; SCr, Serum Creatinine; CrCl, Creatinine Clearance; CAG, Coronary Angiography; PCI, Percutaneous Coronary Intervention; CIN: Contrast-Induced Nephropathy.

Table II. Real time PCR primers.

Certainty assessment							N. of patients		Effect		
N. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CIN	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty
7	Randomised trials	Serious[a]	Not serious	Not serious	Not serious	Publication bias strongly suspected strong association all plausible residual confounding would reduce the demonstrated effect[b]	52/798 (6.5%)	115/792 (14.5%)	RR 0.46 (0.34 to 0.63)	78 fewer per 1,000 (from 96 fewer to 54 fewer)	⊕⊕⊕⊕ HIGH

CI: Confidence interval; RR: Risk ratio. Explanations [a]Inadequate blinding, many studies have unclear allocation concealment and randomization. [b]Asymmetrical Funnel Plot.

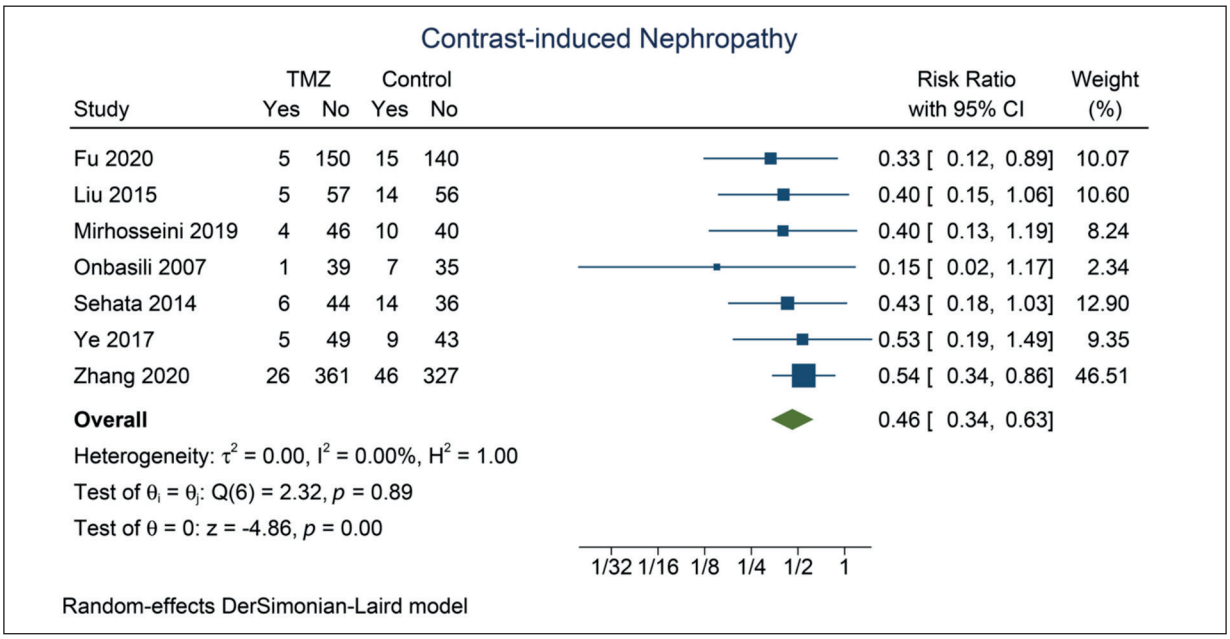

Figure 2. Trimetazidine and contrast-induced nephropathy.

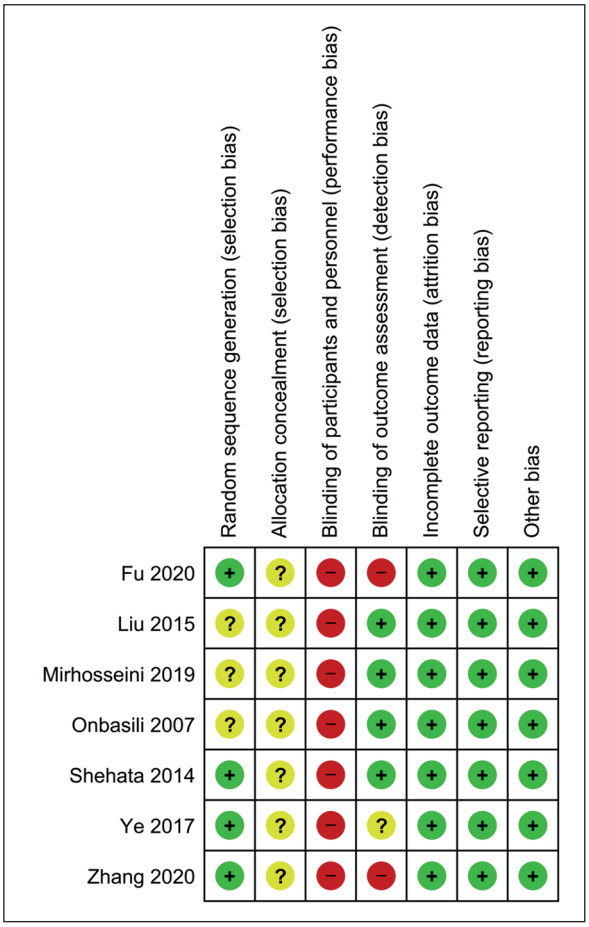

Figure 3. Cochrane risk of bias assessment.

renal insufficiency, with a high certainty of evidence.

Trimetazidine has been shown to attenuate the deleterious effects of ischemia-reperfusion injury at both cellular and mitochondrial levels due to its potent antioxidant activity[23-27]. Since the underlying pathophysiology of CIN involves reactive oxygen species and renal medullar ischemia[28,29], the use of antioxidants such as trimetazidine may counteract the process. Remote ischemia preconditioning and nicorandil, which have been shown to reduce the effect of CIN, works through a similar mechanism[30,31]. Additionally, trimetazidine

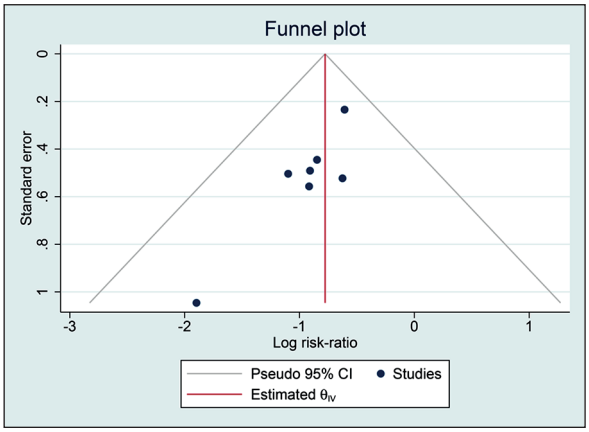

Figure 4. Funnel-plot analysis.

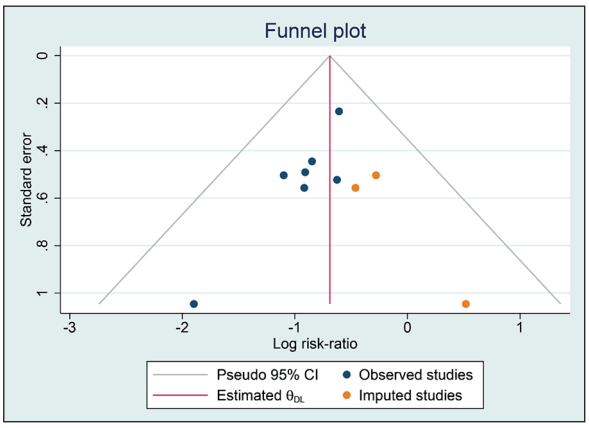

Figure 5. Trim-and-fill analysis.

has been shown to reduce inflammatory mediators in patients undergoing PCI[32].

Meta-regression indicates that trimetazidine's benefit does not vary with age, body mass index, hypertension, diabetes, and ejection fraction. This analysis indicates trimetazidine benefit was observed across broad variety of patients and is not limited to specific patients. Patients without renal insufficiency are underrepresented in the current pooled analysis; this is because most of the studies enrolled patients with renal insufficiency.

Three studies were removed because of the non-randomized design; two of them indicate that trimetazidine does not reduce CIN incidence in unselected patients without targeting the higher-risk patients[33,34]. One study indicates that trimetazidine reduces CIN occurrence in patients with mild-moderate basal renal insufficiency[35]coronary angiography and percutaneous coronary interventions are associated with the highest rates of CIN. Trimetazidine has been described as a cellular anti-ischemic agent. Previous studies demonstrated that Trimetazidine prevents the deleterious effects of ischemia–reperfusion at both the cellular and mitochondrial levels and exerts an anti-oxidant effect. It inhibits excess release of oxygen free radicals, limits cellular acidosis, protects Adenosine Triphosphate (ATP.

Although meta-regression analysis showed that the CIN reducing effect was not significantly influenced by the baseline creatinine level, this might be due to the underrepresentation of patients with high estimated glomerular filtration rate (eGFR). Zhang et al[22] found that trimetazidine reduced CIN occurrence in patients with moderate and high-risk populations based on Mehran score, but not in low-risk patients. Further RCTs are required to confirm whether the effect is demonstrable in patients with normal renal function.

Additionally, the CIN reducing effect of trimetazidine did not vary with contrast media volume. This might be valuable in patients with renal insufficiency receiving a complex coronary intervention, who will be exposed to a large amount of contrast.

One of the concerns of a meta-analysis is publication bias;, the funnel-plot analysis indicates possible publication bias. Trim-and-fill analysis was used to impute three hypothetical studies to "balance" the funnel-plot, and the benefit was still significant, although slightly reduced.

Clinical Implications

Trimetazidine may be administered in patients undergoing CAG/PCI, especially in patients with renal insufficiency. It may be of value in patients with renal insufficiency undergoing complex coronary intervention in which a higher volume of contrast is required. However, due to the underrepresentation of patients without renal insufficiency, further RCTs are required in this subset of patients.

Limitations

The limitation of this systematic review includes the high risk of bias of the individual studies. The randomization process and allocation concealment are often unclear. The blinding is inadequate primarily due to the unavailability of a placebo. Patients without renal insufficiency are underrepresented.

Conclusions

In short, trimetazidine administration decreases the risk of CIN in patients undergoing CAG/PCI, especially in patients with renal insufficiency.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval

Not Applicable. Systematic review and meta-analysis contain data from published studies, not a primary data.

Informed Consent
Not Applicable. Systematic review and meta-analysis contain data from published studies, not a primary data.

Data Availability
The Authors declare that they have no conflict of interests.

Contributorship Statement
Januar Wibawa Martha: conceptualization, investigation, writing—review and editing, supervision. Raymond Pranata: conceptualization, methodology, software, data curation, formal analysis meta-analysis), investigation, validation, writing—original draft, writing—review and editing. Arief Wibowo: data curation, investigation, writing—original draft. Irvan: data curation, investigation, writing—original draft. Rien Afrianti: investigation, writing—review and editing. Mohammad Rizki Akbar: investigation, writing—review and editing.

References

1) 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.
2) 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.
3) 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.
4) Rear R, Bell RM, Hausenloy DJ. Contrast-induced nephropathy following angiography and cardiac interventions. Heart 2016; 102: 638-648.
5) Weisbord SD, Palevsky PM. Prevention of contrast-induced nephropathy with volume expansion. Clin J Am Soc Nephrol 2008; 3: 273-280.
6) Dézsi CA. Trimetazidine in practice: review of the clinical and experimental evidence. Am J Ther 2016; 23: e871-e879.
7) Marzilli M, Vinereanu D, Lopaschuk G, Chen Y, Dalal JJ, Danchin N, Etriby E, Ferrari R, Gowdak LH, Lopatin Y, Milicic D, Parkhomenko A, Pinto F, Ponikowski P, Seferovic P, Rosano GMC. Trimetazidine in cardiovascular medicine. Int J Cardiol 2019; 293: 39-44.
8) Fantini E, Demaison L, Sentex E, Grynberg A, Athias P. Some biochemical aspects of the protective effect of trimetazidine on rat cardiomyocytes during hypoxia and reoxygenation. J Mol Cell Cardiol 1994; 26: 949-958.
9) Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 2000; 86: 580-588.
10) Lopez N, Varo N, Diez J, Fortuno M. Loss of myocardial LIF receptor in experimental heart failure reduces cardiotrophin-1 cytoprotection. A role for neurohumoral agonists? Cardiovasc Res 2007; 75: 536-545.
11) Parang P, Singh B, Arora R. Metabolic modulators for chronic cardiac ischemia. J Cardiovasc Pharmacol Ther 2005; 10: 217-223.
12) Onay-Besikci A, Özkan SA. Trimetazidine revisited: a comprehensive review of the pharmacological effects and analytical techniques for the determination of trimetazidine. Cardiovasc Ther 2008; 26: 147-165.
13) Özden A, Aybek Z, Saydam N, Çalli N, Saydam O, Düzcan E, Güner G. Cytoprotective effect of trimetazidine on 75 min warm renal ischemia-reperfusion injury in rats. Eur Surg Res 1998; 30: 227-234.
14) Grekas D, Dioudis C, Papageorgiou G, Iliadis S, Zilidis C, Alivanis P, Dimitriadou A, Tourkantonis A. Lipid peroxidation after acute renal ischemia and reperfusion in rats: the effect of trimetazidine. Ren Fail 1996; 18: 545-552.
15) 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.
16) Fu H, Zhang J, Zhang H, Zhang P, Fu X, Zeng Z, Zhang X, Li W, Yang S, Liu X, Fu N. Trimetazidine can prevent the occurrence of contrast-induced nephropathy after percutaneous coronary intervention in elderly patients with renal insufficiency. Perfusion 2020 Sep 10; 267659120957856. doi: 10.1177/0267659120957856. Online ahead of print.
17) Liu W, Ming Q, Shen J, Wei Y, Li W, Chen W, Xu Y. Trimetazidine prevention of contrast-induced nephropathy in coronary angiography. Am J Med Sci 2015; 350: 398-402.
18) Mirhosseini A, Farahani B, Gandomi-Mohammadabadi A, Keyvani H, Biglari-Abhari M, Davari A, Vazirizadeh-Mahabadi M, Savaj S. Preventive effect of trimetazidine on contrast-induced acute kidney injury in CKD patients based on urinary neutrophil gelatinase-associated lipocalin (uNGAL): a randomized clinical trial. Iran J Kidney Dis 2019; 13: 191-197.
19) Onbasili AO, Yeniceriglu Y, Agaoglu P, Karul A, Tekten T, Akar H, Discigil G. Trimetazidine in the

prevention of contrast-induced nephropathy after coronary procedures. Heart 2007; 93: 698-702.

20) Shehata M. Impact of trimetazidine on incidence of myocardial injury and contrast-induced nephropathy in diabetic patients with renal dysfunction undergoing elective percutaneous coronary intervention. Am J Cardiol 2014; 114: 389-394.

21) Ye Z, Lu H, Su Q, Xian X, Li L. Effect of trimetazidine on preventing contrast-induced nephropathy in diabetic patients with renal insufficiency. Oncotarget 2017; 8: 102521-102530.

22) Zhang X, Zhang P, Yang S, Li W, Men X, Fu N. Preventive effect of trimetazidine on contrast-induced nephropathy undergoing percutaneous coronary intervention in elderly moderate and high risk diabetics stratified by mehran score. Perfusion 2020 Aug 24;267659120952057. Doi: 10.1177/0267659120952057. Online ahead of print.

23) Elimadi A, Settaf A, Morin D, Sapena R, Lamchouri F, Cherrah Y, Tillement JP. Trimetazidine counteracts the hepatic injury associated with ischemia-reperfusion by preserving mitochondrial function. J Pharmacol Exp Ther 1998; 286: 23-28.

24) Aubert A, Bernard C, Clauser P, Harpey C, Vaudry H. Effect of phenazine methosulfate on electrophysiological activity of the semicircular canal: antioxidant properties of trimetazidine. Eur J Pharmacol 1989; 174: 215-225.

25) Wu S, Chang G, Gao L, Jiang D, Wang L, Li G, Luo X, Qin S, Guo X, Zhang D. Trimetazidine protects against myocardial ischemia/reperfusion injury by inhibiting excessive autophagy. J Mol Med 2018; 96: 791-806.

26) Park JH, Jun JH, Shim JK, Shin EJ, Shin E, Kwak YL. Effects of post ischemia-reperfusion treatment with trimetazidine on renal injury in rats: Insights on delayed renal fibrosis progression. Oxid Med Cell Longev 2018; 2018: 1072805.

27) Amini N, Sarkaki A, Dianat M, Mard SA, Ahangarpour A, Badavi M. The renoprotective effects of naringin and trimetazidine on renal ischemia/reperfusion injury in rats through inhibition of apoptosis and downregulation of micoRNA-10a. Biomed Pharmacother 2019; 112: 108568.

28) Wong PCY, Li Z, Guo J, Zhang A. Pathophysiology of contrast-induced nephropathy. Int J Cardiol 2012; 158: 186-192.

29) Geenen RWF, Kingma HJ, van der Molen AJ. Contrast-induced nephropathy: pharmacology, pathophysiology and prevention. Insights Imaging 2013; 4: 811-820.

30) 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.

31) 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.

32) Hao J, Du H, Li W, Zhao Z, Liu F, Lu J, Yang X, Cui W. Effects of atorvastatin combined with trimetazidine on myocardial injury and inflammatory mediator in unstable angina patients during perioperative of percutaneous coronary intervention. Eur Rev Med Pharmacol Sci 2015; 19: 4642-4646.

33) Galal H, Shehta M, Attia S, Bastawy I. Comparing trimetazidine with allopurinol in prevention of contrast induced nephropathy after coronary angiography. J Saudi Hear Assoc 2020; 32: 451-455.

34) Lian X, He W, Zhan H, Chen J, Tan N, He P, Liu Y. The effect of trimetazidine on preventing contrast-induced nephropathy after cardiac catheterization. Int Urol Nephrol 2019; 51: 2267-2272.

35) Ibrahim TA, El-Mawardy RH, El-Serafy AS, El-Fekky EM. Trimetazidine in the prevention of contrast-induced nephropathy in chronic kidney disease. Cardiovasc Revascularization Med 2017; 18: 315-319.