Efficacy of Trimetazidine on Prevention of Contrast Induced Nephropathy in Elderly Patients Undergoing Coronary Angiogram and/or Angioplasty: A Systematic Review and Meta- Analysis of Randomized Clinical Trials

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Background. As cardiac interventional medicine continues to advance, the occurrence of contrast-induced nephropathy (CIN) is on the rise each year. Trimetazidine, an anti-ischemic medication, has shown a noteworthy capability to reduce the occurrence of CIN. A systematic review and meta-analysis were carried out to assess trimetazidine's clinical impact in preventing CIN in patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI), regardless of the trimetazidine dose given. This meta-analysis aims to strengthen the latest data on the significance of administering a specific dose of oral trimetazidine (35 mg/tab twice daily for 72 hours) on elderly patients for prevention of CIN.

Methods. A systematic review was conducted to find clinical trials that assess trimetazidine's impact on the occurrence of CIN in elderly patients undergoing CAG/PCI up to January 2023. The search was carried out on databases including PubMed, Scopus, and Google Scholar. All were elderly patients (age >50 years) given oral trimetazidine 35 mg/tab twice daily for 72 hours, and the outcome of interest was the occurrence of CIN, decrease in serum creatinine, and improvement in creatinine clearance.

Results. The analysis of serum creatinine levels at various post-procedure time points revealed differing outcomes. At 24 hours post procedure, the trimetazidine group exhibited a significant average decrease of 0.09 mg/dL compared to control groups (95% CI -0.14, -0.03; p=0.003), with minimal heterogeneity. However, at 48 and 72 hours post procedure, the evidence was inconclusive, with varying levels of heterogeneity, suggesting result variability. A comprehensive analysis of all available studies indicated an average serum creatinine reduction of 0.13 mg/dL in the trimetazidine group, with statistical significance, although substantial heterogeneity was observed. Creatinine clearance at 72 hours post procedure showed an average increase in the trimetazidine group and minimal heterogeneity was present. An analysis of CIN rates across six studies demonstrated a risk ratio of 0.55, indicating a 45% reduction in CIN risk with trimetazidine, and a risk difference of 0.07, signifying 7 fewer expected CIN cases per 100 individuals treated with trimetazidine, with minimal heterogeneity observed in both analyses.

Conclusion. Administering trimetazidine 35 mg/tab twice daily for 72 hours significantly decreases CIN risk in elderly patients undergoing CAG/PCI.

Keywords. *Trimetazidine, Contrast-induced nephropathy, Contrast-induced kidney injury*

Introduction

Contrast-induced nephropathy (CIN) is a common and potentially serious complication that can follow the administration of iodinated contrast media to patients at risk of acute renal injury.[1] Among all procedures utilizing contrast media for diagnostic or therapeutic purposes, coronary angiography (CAG) and percutaneous coronary intervention (PCI) are associated with the highest rates of CIN.[4] The increasing adoption of imaging and interventional techniques, such as CAG/PCI, which

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require the use of intravascular contrast agents will markedly raise the potential for patients to develop CIN.

In studies, CIN is defined as the impairment of renal function, measured as either 25% increase in serum creatinine (SCr) from baseline or 44 µmol/L increase in absolute SCr within 72 hours of intravenous contrast administration.[3] The reported incidence of CIN varies depending on the patient population studied. Studies have shown that the incidence of CIN in elderly patients with coronary heart disease receiving PCI was as high as 19.51%.[2] Therefore, prevention must be taken to avoid nephrotoxicity caused by contrast media.

Several randomized clinical trials (RCTs) have shown trimetazidine to be effective in preventing contrast-induced renal dysfunction following the administration of contrast media during CAG/PCI. Different dosages of trimetazidine were used in different RCTs.[5-7] Some studies used trimetazidine 20 mg/tab thrice daily; other studies used trimetazidine 35 mg/tab twice a day due to its better availability and its enhancement of a more compliant use.[8] This meta-analysis aims to assess and focus on the impact of administering a specific dose of oral trimetazidine (35 mg/tab twice daily for 72 hours) on elderly patients for prevention of CIN.

Objectives

The primary objective of this meta-analysis is to compare the clinical efficacy of trimetazidine 35 mg/tab twice daily and standard parenteral hydration for 72 hours in prevention of CIN in elderly patient undergoing CAG/PCI.

Secondary objectives include (a) to compare the SCr level and creatinine clearance (CrCl) at various post-procedure time points (24 hours, 48 hours, 72 hours post procedure) and (b) to compare the rate of CIN patients undergoing CAG/PCI who were given trimetazidine.
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Statement of the Problem

This meta-analysis sought to answer the question, "Is trimetazidine 35 mg/tab twice daily effective in preventing the occurrence of CIN in elderly patients undergoing CAG and/or PCI?"

Definition of Terms

- CIN – impairment of renal function, measured as either 25% increase in SCr from baseline or 44 µmol/L increase in absolute SCr within 72 hours of intravenous contrast administration.
- Trimetazidine – a cellular anti-ischemic agent that has been shown to prevent the deleterious effects of ischemia reperfusion at both the cellular and mitochondrial levels and exerts an anti-oxidant effect. It inhibits excessive release of oxygen free radicals, limits cellular acidosis, protects adenosine triphosphate stores, reduces membrane lipid peroxidation, and inhibits neutrophil infiltration

Methodology

Search History

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline, a systematic review was conducted to find clinical trials that assess trimetazidine's impact on the occurrence of CIN in patients undergoing CAG or PCI. The researchers systematically searched health-related electronic databases, including PubMed, Cochrane Library, and Google Scholar from inception to January 2023 using the following medical subject headings AND/OR entry words in any field: "Trimetazidine", "Normal Saline Solution", "Contrast induced nephropathy", "Contrast Induced Acute Kidney Injury" (Table 1).

Intervention Outcomes

The intervention was trimetazidine 35 mg/tab twice daily initiated before CAG and/or PCI. The control was standard of care. The main outcome is incidence of CIN, defined as the increase in SCr level ≥0.5 mg/dL (44.2 mmol/L) or >25% of the baseline value 48–72 hours after contrast media administration.

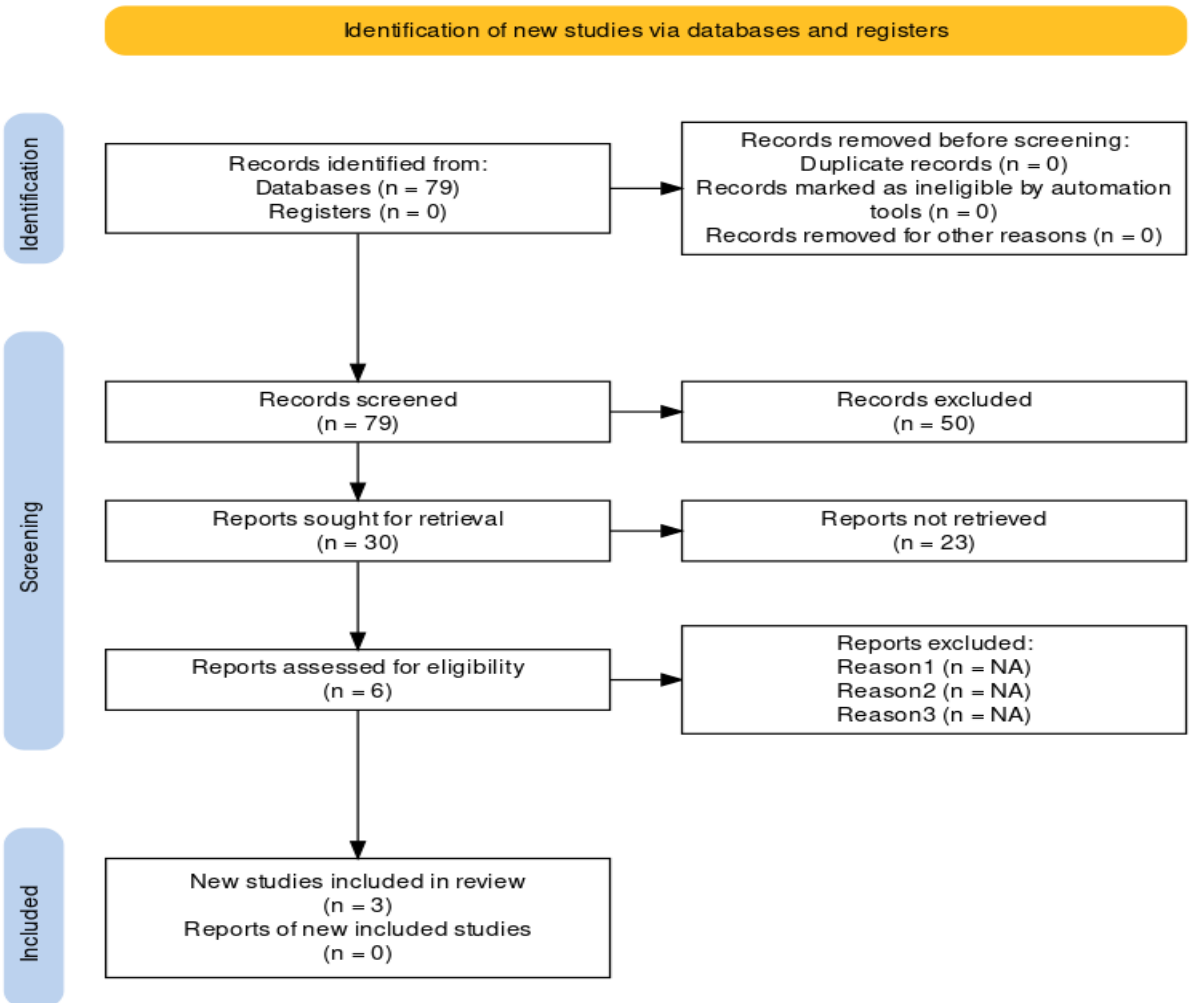
Study Selection

Two researchers independently conducted a search on PubMed, Google Scholar, and Scopus database until January 2023. A total of 79 studies were collected from prominent databases. Duplicates were eliminated. Identified studies were meticulously reviewed. After applying inclusion and exclusion criteria, 73 studies were removed from the analysis, and 6 studies were considered for qualitative synthesis (Figure 1).

Table 1. Eligibility criteria

Inclusion Criteria	Exclusion Criteria
• Studies performed as RCT published in English • Patients >50 years old • Intervention treatment given are oral trimetazidine (35 mg/tab twice daily for 72 hours) vs standard hydration • Outcome reports the incidence of CIN	• Patients with severe renal impairment defined as eGFR <30 • Patients <50 years old • Intervention treatment given are oral trimetazidine (20 mg/tab twice daily for 96 hours or 72 hours) vs standard hydration • Non-English articles • Case reports, review articles

Figure 1. Selection process (PRISMA flowchart)



Data Extraction

The researcher conducted data extraction for several variables, such as the primary author, publication year, research methodology, sample size, patient baseline characteristics, trimetazidine dose, the description of CIN, and the occurrence rate of CIN (Table 2, Table 3).

Quality Assessment

The assessment of potential bias was conducted using the Cochrane Risk of Bias tool. The authors examined the literature to evaluate the following aspects: (1) how random sequences were generated; (2) the concealment of allocation; (3) whether patients and researchers were blinded; (4) if outcome assessments were performed without bias; (5) the handling of incomplete data; (6) whether there was selective reporting of outcomes; and (7) any other potential sources of bias. A checklist was created, and the included studies were categorized as having a low, unclear, or high risk of bias based on this assessment.

Table 2. Characteristics of studies included in meta-analysis

Study	Population	Intervention	Control	Outcome
Galal et al. (2020)	80	Trimetazidine 35 mg/tab, 1 tab twice daily for 72 hours + standard parenteral hydration	Standard parenteral hydration	SCr, CrCl, rate of CIN

Hadi et al. (2020)	89	Trimetazidine 35 mg/tab, 1 tab twice daily for 72 hours + standard parenteral hydration	Standard parenteral hydration	Rate of CIN (missing data for other parameters; effect measures only)
Zhang et al. (2020)	760	Trimetazidine 35 mg/tab, 1 tab twice daily for 72 hours + standard parenteral hydration	Standard parenteral hydration	SCr, CrCl, rate of CIN
Mirhosseini et al. (2019)	100	Trimetazidine 35 mg/tab, 1 tab twice daily for 72 hours + standard parenteral hydration	Standard parenteral hydration	SCr, rate of CIN
Ibrahim et al. (2017)	100	Trimetazidine 35 mg/tab, 1 tab twice daily for 72 hours + standard parenteral hydration	Standard parenteral hydration	SCr, CrCl, rate of CIN
Shehata et al. (2014)	100	Trimetazidine 35 mg/tab, 1 tab twice daily for 72 hours + standard parenteral hydration	Standard parenteral hydration	SCr, CrCl, rate of CIN

Table 3. Baseline characteristics of patients enrolled in studies included in the meta-analysis

	Shehata et al. (2014)		**Ibrahim et al. (2017)**		**Mirhosseini et al. (2019)**		**Galal et al. (2020)**		**Hadi et al. (2020)**		**Zhang et al. (2020)**	
	TZD	**CTRL**	**TZD**	**CTRL**	**TZD**	**CTRL**	**TZD**	**CTRL**	**TZD**	**CTRL**	**TZD**	**CTRL**
N	50	50	50	50	50	50	40	40	44	45	387	373
Age	58 (6)	59 (5)	64.83 (7.36)	62.88 (8.30)	65 (6)	67 (6)	61.10 (11.16)	58.63 (9.63)	64.4 (8.1)	64.9 (7.7)	67.23 (6.87)	67.37 (6.37)
Sex												
Male	35 (70.0)	33 (66.0)	27 (54.0)	30 (60.0)	20 (40.0)	24 (48.0)	30 (75.0)	29 (72.5)	23 (52.3)	28 (62.2)	273 (70.05)	254 (68.1)
Female	15 (30.0)	17 (34.0)	23 (46.0)	20 (40.0)	30 (60.0)	26 (52.0)	10 (25.0)	11 (27.5)	21 (47.7)	17 (37.8)	114 (29.5)	119 (31.9)
Weight												
Weight	–	–	78.52 (14.66)	77.18 (10.04)	66 (6)	68 (5)	–	–	–	–	–	–
BMI	27 (3)	28 (3)	–	–	–	–	–	–	–	–	24.88 (2.62)	24.97 (1.92)
Comorbidities												
HTN	23 (46.0)	25 (50.0)	30 (60.0)	34 (68.0)	34 (68.0)	28 (56.0)	25 (62.5)	23 (57.5)	43 (97.7)	43 (95.6)	157 (40.6)	143 (38.3)
DM	–	–	26 (52.0)	31 (62.0)	32 (64.0)	31 (62.0)	19 (47.5)	27 (67.5)	44 (100.0)	45 (100.0)	–	–
Smoking	15 (30.0)	16 (32.0)	33 (66.0)	26 (52.0)	–	–	22 (55.0)	28 (70.0)	19 (43.2)	22 (48.9)	–	–
Ejection fraction	54 (8)	55 (7)	51.22 (6.50)	51.96 (9.99)	51 (4)	51 (5)	49.50 (10.25)	47.85 (8.75)	–	–	58.85 (8.23)	60.08 (8.28)

Baseline Cr	2 (0.5)	2 (0.4)	1.56 (0.22)	1.57 (0.24)	1.27 (0.15)	1.29 (0.15)	1.33 (0.36)	1.36 (0.32)	1.53	1.55	0.90 (0.27)	0.88 (0.30)
Baseline CrCl/eGFR	47 (16)	50 (15)	54.02 (13.02)	50.55 (12.18)	50 (7)	50 (8)	67.45 (13.95)	65.23 (16.14)	42.82	44.2	72.12 (12.87)	71.79 (14.07)
Contrast												
Volume (mL)	270 (10)	280 (15)	112.80 (67.52)	124.40 (40.01)	–	–	184.75 (53.68)	186.63 (72.39)	132.4 (44.1)	138.6 (38.3)	172.79 (74.01)	167.82 (58.75)
Dosage (mL/min)	–	–	–	–	116.80	121.80	–	–	–	–	–	–

Statistical Analysis

The statistical analysis was conducted using Cochrane Review Manager (RevMan) 5. The data were analyzed using the inverse-variance approach and a random effects model. The results were presented in terms of risk ratio (RR) and risk difference (RD) for dichotomous data, and as mean differences (MDs) for continuous data. In cases where data were presented as medians and interquartile ranges, estimates of means and standard deviations were calculated using methods outlined by McGrath et al. (2020), which are suitable for non-normal and skewed data.

For the study by Hadi et al. (2020), missing data were imputed using the provided effect measure and p-value, following the guidelines from section 6.5.2.3 of the Cochrane Handbook for Systematic Reviews of Interventions.

In the case of the paper by Zhang et al. (2020), participant data were stratified based on risk groups defined by Mehran scores. To facilitate analysis, the subgroups were combined using the methodology outlined in section 6.5.2.10, "Combining groups," from the Cochrane Handbook.

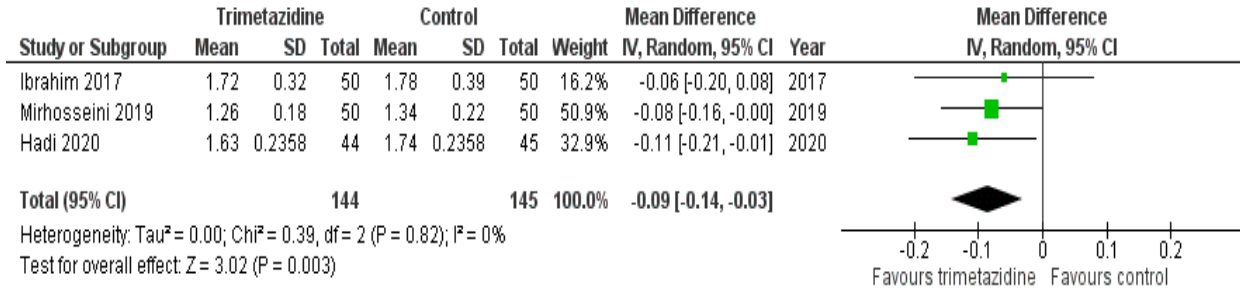
The analysis of reductions in SCr was initially stratified based on follow-up time (24, 48, and 72 hours post procedure). Effect measures with corresponding standard errors were extracted from these time points to create a composite analysis for the impact of the intervention on SCr, incorporating all available studies. When papers provided multiple sets of data (e.g., for different follow-up periods), only the data from the latest follow-up were utilized to prevent unit-of-analysis errors.

Statistical significance was defined as $p<0.05$, and statistical heterogeneity was assessed using the chi-square and Higgin's I^2 statistic. Heterogeneity values were classified as minimal, moderate, substantial, and considerable for scores falling within the ranges of 0–40%, 30–60%, 50–90%, and 75–100%, respectively, following the guidelines provided in the Cochrane Handbook.

Results

Serum creatinine levels measured at different post-procedure time points yielded varying results. At 24 hours post procedure, the trimetazidine group showed a significant average decrease of 0.09 mg/dL compared to control groups (95% CI -0.14, -0.03; p = 0.003), with minimal heterogeneity (I^2=0%, p=0.82; Figure 2).

Figure 2. SCr 24 hours post procedure



However, analyses at 48 hours (MD=-0.07, 95% CI -0.18, 0.05; p=0.26; Figure 3) and 72 hours (MD=-0.16, 95% CI, -0.38, 0.07; p=0.18; Figure 4) post procedure did not provide conclusive evidence, and both exhibited varying levels of heterogeneity (I^2=69%, p=0.07, Figure 3; I^2=80%, p=0.002, Figure 4), indicating result variability.

Figure 3. SCr 48 hours post procedure

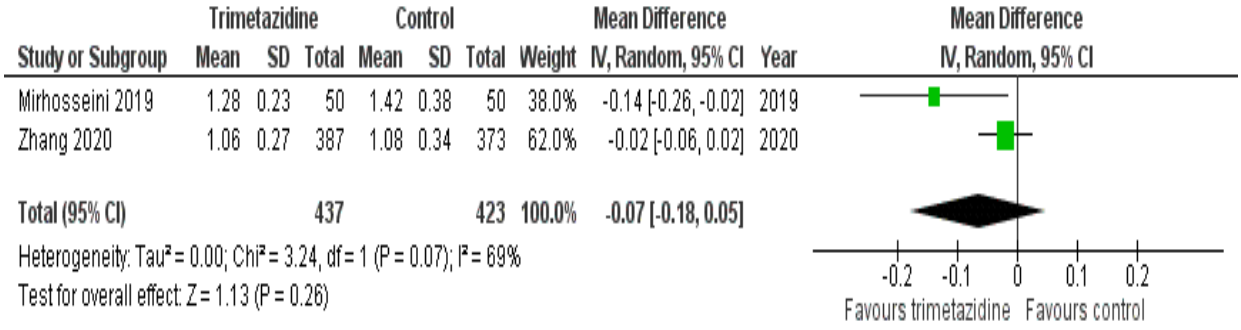
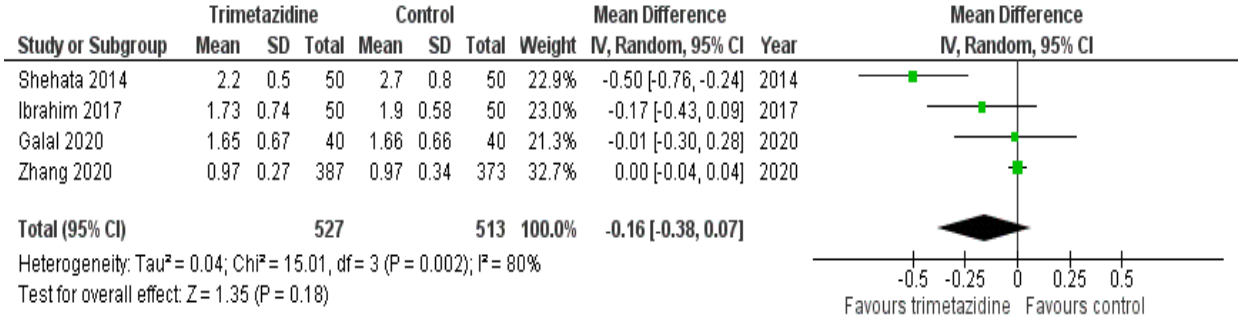


Figure 4. SCr 72 hours post procedure



A comprehensive analysis using all available studies indicated an average SCr reduction of 0.13 mg/dL in the trimetazidine group, with statistical significance (95% CI -0.24, -0.02; p=0.02; Figure 5). Substantial heterogeneity was observed in this analysis (I^2=78%, p=0.0005, Figure 5).

Creatinine clearance measured at 72 hours post procedure showed an average increase of 3.60 mL/minute in the trimetazidine group compared to the control (95% CI 1.30, 5.90; p=0.002; Figure 6), with minimal heterogeneity (I^2=23%, p=0.27, Figure 6).

Figure 5. SCr post procedure

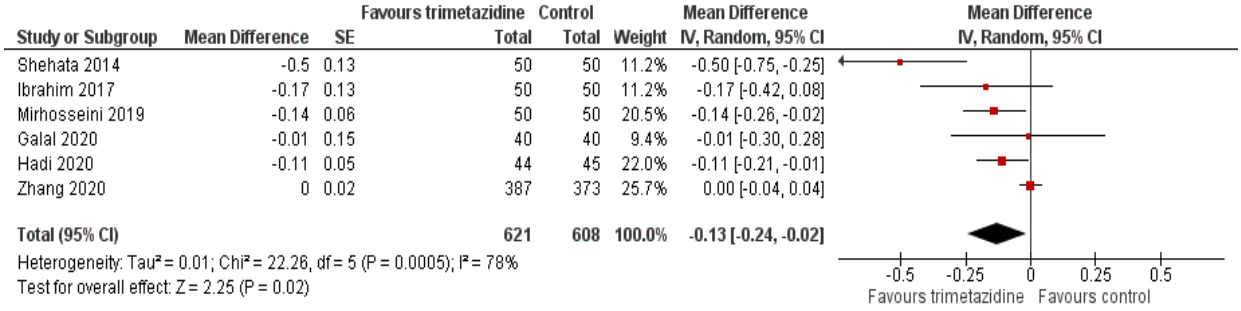


Figure 6. CrCl 72 hours post procedure

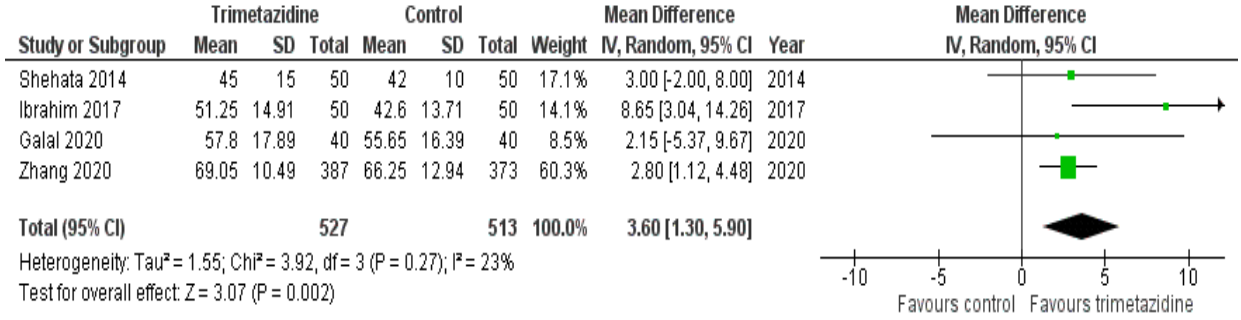


Figure 7. RR CIN

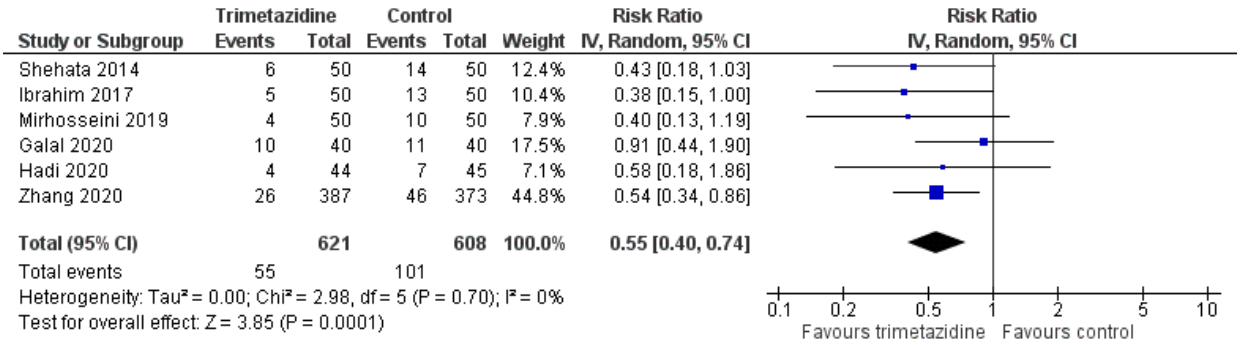
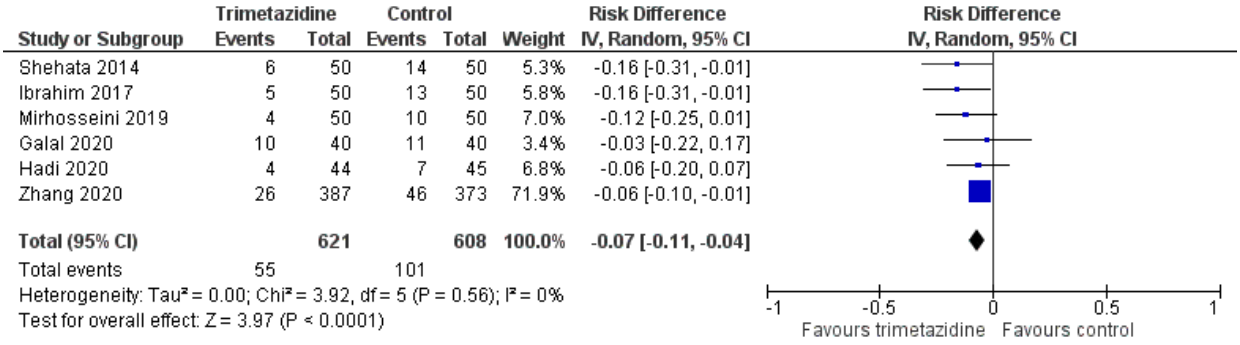


Figure 8. RD CIN



An analysis of CIN rates across all six studies demonstrated RR of 0.55 in the intervention group compared to the control (95% CI 0.40, 0.74; p=0.0001; Figure 7), equivalent to a 45% reduction in the risk of CIN for individuals receiving trimetazidine. Additionally, RD of 0.07 was calculated (95% CI -0.11, -0.04; p=0.0001; Figure 8), translating to seven fewer expected cases of CIN per 100 individuals treated with trimetazidine. Minimal heterogeneity was observed for both RR and RD analyses (I^2=0%, p=0.70, Figure 7; I^2=0%, p=0.56, Figure 8).

Discussion

CIN remains a significant concern for individuals with pre-existing kidney issues, especially in those undergoing PCI and dealing with renal problems. The risk of CIN is heightened in these cases. Recent data underscores the gravity of CIN, as it is associated with increased immediate in-hospital and 30-day mortality rates, along with a gradual and persistent decline in renal function. CIN is a severe complication that may occur following coronary angiography, carrying a heightened risk of mortality and health complications. This includes the potential need for short-term hemodialysis, extended hospitalization, and lasting kidney damage. CIN is more commonly observed in individuals with pre-existing chronic kidney problems, particularly in those with diabetes, dehydration, and congestive heart failure. Furthermore, the use of higher contrast medium doses and intravascular injection of contrast agents is linked to a greater likelihood of CIN.[5-10] Research has reported CIN occurrence in 11% to 44% of patients with moderate renal insufficiency, and the severity of pre-existing kidney dysfunction serves as the most significant independent predictor of CIN, directly affecting the likelihood of its occurrence.

Although the use of normal saline for hydration has proven effective in reducing CIN, recent findings suggest that combining trimetazidine with hydration, as opposed to hydration alone, offers advantages in safeguarding renal function. Various studies have explored the potential benefits of N-acetylcysteine, $NaHCO_3$, vitamin C, calcium channel blockers, and statins, but the results have been inconsistent, and there is inconclusive data regarding their renal-protective effects.

Trimetazidine, known for its role as an anti-anginal agent, operates by enhancing myocardial glucose utilization through the inhibition of fatty acid metabolism. Given its pharmacological properties, it is considered a promising option for preventing CIN. Previous animal studies have demonstrated that trimetazidine reduces malondialdehyde levels, resulting in decreased lipid peroxidation and, consequently, a reduction in oxygen free radical-induced renal damage.

This study presents several notable advantages over previous meta-analyses. First, it benefits from a better availability of data regarding the 35 mg dose of trimetazidine, as reported in one article. Second, it maintains a consistent dose of trimetazidine throughout the analysis, a factor that was not consistently controlled for in other meta-analyses. Third, this study includes more recent trials that were not considered in prior meta-

analyses, ensuring the incorporation of the latest evidence. Lastly, it broadens the scope of outcomes by encompassing a range of parameters, including CIN, SCr, and CrCl, providing a more comprehensive view of the intervention's impact.

Conclusion

The combined findings consistently demonstrated that the use of 35 mg of trimetazidine administered twice daily, in conjunction with normal saline hydration, consistently lowered the occurrence of CIN, decreased SCr, and improved CrCl in individuals with renal insufficiency who were undergoing PCI.

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