The Efficacy of Oral Trimetazidine in Preventing Contrast-Induced Nephropathy Among Patients Undergoing Elective Coronary Procedures: A Meta-analysis of Randomized Controlled Trials

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Abstract

Introduction: Contrast-induced nephropathy (CIN) is a serious but preventable complication of coronary procedures. Trimetazidine (TMZ) has recently been explored for use in preventing post-procedural CIN due to its cellular anti-ischemic and antioxidant properties. The objective is to assess the efficacy of oral TMZ in the prevention of contrast induced nephropathy during elective coronary angiography and PCI among patients with renal impairment.

Methods: We conducted a systematic search of the Cochrane Central Register of Controlled Trials, Pubmed/MEDLINE, EMBASE, clinicaltrials.gov for articles published until June 2016 for randomized controlled trials examining the effects of adding oral TMZ to standard therapy in preventing CIN. Outcome measures were incidence of CIN, defined as a 0.5 mg/dl or ≥25% increase in serum creatinine 48-72 hours after contrast exposure, and incidence of dialysis-requiring CIN. Validity of studies was assessed through a risk assessment tool available from Cochrane. Treatment effect was estimated by calculating the Mantel-Haenszel-weighted risk ratio (RR) using a fixed-effects model available from RevMan 5.3.

Results: A total of four studies comprising 714 patients (TMZ group=352, Control group=362) were included in the final analysis. Pooled results revealed the TMZ group was associated with significantly fewer incidences of CIN compared to control (RR 0.33, 95% confidence interval (CI), 0.20, 0.53; *P*<.00001), with a relative risk reduction of 67% and an absolute risk reduction of 11.04% (NNT=nine). No dialysis-requiring CIN was observed in the included studies.

Conclusion: The addition of oral TMZ to standard hydration confers a significant benefit in preventing CIN after coronary procedures among patients with mild to moderate renal impairment. We recommend the addition of TMZ to standard prevention strategies. However, a large well-designed trial should be conducted to determine its effect on other outcomes such as prevention of dialysis-requiring CIN and mortality.

Keywords: oral trimetazine, contrast-induced nephropathy, elective coronary procedures

Introduction

Contrast-induced nephropathy (CIN), defined as an increase in the baseline serum creatinine concentration (SCr) by ≥25% or 0.5 mg/dl 48-72 hours after contrast exposure,[1] is a serious but preventable complication of coronary angiogram and percutaneous coronary interventions (PCI), occurring in as many as three to 24% who undergo such procedures despite existing methods of prevention.[2–4] Several authors have found that even transient elevations of serum creatinine is associated with increased morbidity and mortality, longer hospital stays, greater health expenditures and increased incidence of chronic renal failure.[5–9] While Manske, Sprafka, Strony and Wang found that as much 15% of patients with CIN required short-term hemodialysis,[10] Freeman et al., reported a low incidence of dialysis requiring CIN (<0.5%).[9] Nevertheless, in their cohort, patients who required dialysis had a significantly greater mortality rate than those who did not (39% vs. 1.4%, *p*<0.001). Patients with pre-existing renal impairment and significant comorbidities are at higher risk for CIN, with prevalence rising to as high as 50% in patients with pre-existing renal disease or diabetes.[10,11]

The mechanism of injury is not yet fully understood but is theorized to be due to either renal medullary hypoxia or direct cellular toxicity from cytokine-mediated release of free radicals and oxidative stress .[7,12,13] The role of volume depletion and the resulting depressed activity of anti-oxidants and renal medullary ischemic injury have been implicated.[14]

Trimetazidine (TMZ) is a widely used anti-anginal agent that has anti-oxidant properties lending a protective effect against free-radical damage. On the postulation that the pathogenesis of CIN can be attributed to medullary ischemia

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and generation of reactive oxygen species, TMZ has thus been explored as a possible preventive strategy.[15] Such a benefit was demonstrated in one animal study in which fewer signs of glomerular and kidney damage were found rats treated with TMZ prior to contrast exposure.[16]

Standard practice in the prevention of contrast-induced nephropathy involves volume expansion with crystalloids beginning three to 12 hours prior and up to six to 12 hours after contrast exposure.[17,18] Other interventions used for the prevention of CIN include reduction of contrast volume and use of non-ionic hypo-osmolar contrast agents. Administration of medications such as statins, N-acetylcysteine (NAC), ascorbic acid and sodium bicarbonate have been explored as well, however the strength and quality of evidence for many of these interventions are lacking.[3,17–20] Trimetazidine (TMZ) is another widely accessible intervention that has been shown to have an added benefit in several small randomized controlled trials.[21–23] This is an update of a previous meta-analysis published in 2015 by Nadkarni et al.[24], which had inconclusive results due to the small number of studies and small sample size involved. Since then, an additional study has been conducted by Liu et al.[25] which could add robustness to currently available data.

Research question

Among adult patients with renal impairment undergoing elective percutaneous coronary procedures, how effective is oral trimetazidine compared to placebo, in addition to standard therapy, in preventing contrast-induced nephropathy?

Specific objectives

To determine the efficacy of oral trimetazidine compared to placebo in reducing renal morbidity among patients with renal impairment undergoing elective coronary procedures in terms of:

a. incidence of CIN, defined as an increase in serum creatinine (SCr) by ≥25% or 0.5 mg/dl from baseline 48-72 hours after contrast exposure

b. incidence of dialysis-requiring CIN

Methods

Criteria for considering studies for this review

1. Types of studies - We included randomized controlled trials that compared the effects of adding TMZ vs. placebo to standard treatment in preventing CIN in a population of patients with renal impairment undergoing either coronary angiography +/- PCI. We included all studies with original data on at least our target primary outcome. No language constraints were applied.
2. Types of participants - Study participants included adult patients with renal impairment who underwent elective coronary angiography and/or PCI.
3. Types of interventions - We included trials that compared the effect of the addition of oral TMZ versus placebo on top of standard therapy, which involved volume expansion with 1.0 – 1.5 mL/kg/hr of isotonic crystalloid for three to 12 hours prior to until six to 12 hours after contrast exposure.
4. Types of outcome measures
   - Primary outcomes - We included studies with outcome measures of incidence of CIN, defined as either an increase in serum creatinine by 0.5 mg/dL or 25% from baseline values 48-72 hours post-procedure.
   - Secondary outcomes - We searched for studies with data on the incidence of dialysis-requiring CIN.

Search methods for identification of studies

The two authors independently searched the Cochrane Central Register of Controlled Trials, Pubmed/MEDLINE, EMBASE, clinicaltrials.gov for articles published until June 2016 for randomized controlled trials examining the effects of adding oral TMZ to standard therapy in preventing CIN. We employed a strategy of using three comprehensive search themes combined with the boolean operator "OR". For the theme "coronary angiography", we used combination of MeSH, entry terms and text words for "coronary angiogra*", "coronary angiography" & "percutaneous coronary intervention". For the theme "acute kidney injury", we used renal failure, contrast nephropathy, acute kidney injury & kidney. For the theme "contrast media", we used contrast & contrast media. The search result was then combined with the term "Trimetazidine" using the boolean operator "AND". No language restrictions were imposed. The investigators reviewed all relevant articles, with any discrepancies resolved by consensus.

Searching other resources

The reference lists of relevant articles were perused to search for any studies we might have missed. Studies citing the RCTs and the meta-analysis were also sought. Pharmaceutical companies involved in manufacturing TMZ were contacted to request for any unpublished trials. Unfortunately, the authors were not able identify or contact any local authority who is currently conducting research on the topic.

Data collection and analysis

Collected articles were independently screened and evaluated by two authors (AR & KR) and differences in judgment were settled by consensus. Data was extracted using a data collection form. Analysis was performed in accordance with the Cochrane Collaboration guidelines.[26]

Data obtained was transcribed onto data collection forms and analyzed using Revman 5.3.

Selection of studies

Studies included all prospective, randomized controlled trials investigating the efficacy of peri-procedural administration of oral TMZ in preventing CIN, compared to standard treatment involving hydration with isotonic fluids. We included only studies with available data on the baseline and post-procedural (48-72 hours post-procedure) serum creatinine values.

Data extraction and management

The two authors independently extracted the data of included studies using a data extraction sheet, which included publication year, details on trial participants (number per treatment group, mean age, baseline creatinine and presence of diabetes), description of the intervention including trimetazidine dose, interval between administration and coronary procedure, primary outcome (creatinine clearance) including timing of measurement, secondary outcomes, and study results.

Assessment of risk of bias in included studies

A risk assessment tool available from Cochrane was used to assess for the validity and risk of bias of included studies. Differences in assessment were settled by consensus.

Measures of treatment effect

We calculated the risk ratio to compare the benefit of adding TMZ vs. placebo to standard therapy in preventing CIN.

Dealing with missing data

We attempted to contact the authors of the RCTs with missing data.

Assessment of heterogeneity

The I^2 statistic was used to estimate heterogeneity between trials.

Assessment of reporting biases

Screened articles were assessed using a risk assessment tool available from the Cochrane library. Both authors performed quality assessment independently. Disagreements were resolved by consensus.

Data synthesis

We estimated treatment effects by calculating the Mantel-Haenszel-weighted risk ratio (RR) using a fixed-effects model of data analysis available with RevMan 5.3. This was deemed ideal as the rates of CIN were low and the collective sample size of included studies was low.

Results

The initial search strategy yielded a total of 135 articles until June 2016. Ten studies were deemed relevant to our research question, of which five are RCTs. We excluded one study because it did not use the universal definition of CIN (observed for up to seven days post-exposure, no data on Scr at 48-72 hours) (Figure 1).

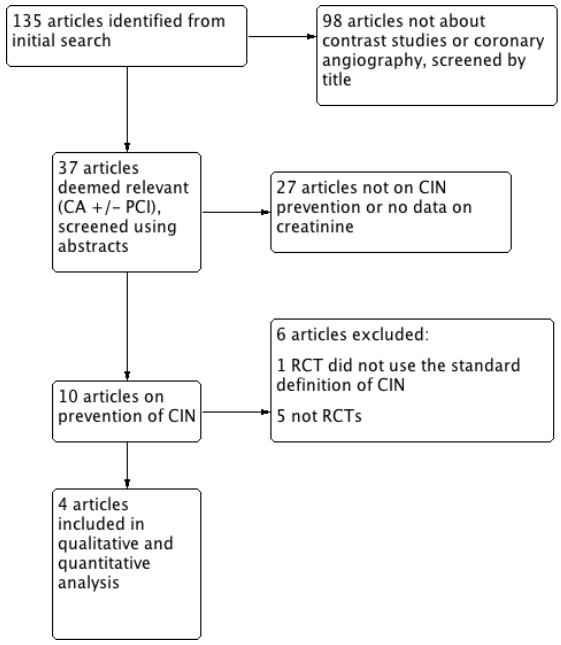

Figure 1. Preferred reporting items for systematic reviews and meta-analysis flow chart of the included studies.

Included studies

Four RCTs were included in the final analysis. Risk of bias assessment of individual studies are summarized in Figure 2. The characteristics of included studies are illustrated Table I. The overall analysis included 714 patients (352 for TMZ plus standard therapy and 362 for placebo). All participants had mild to moderate CKD (serum creatinine of 1.2-2.5 mg/dL or eGFR 30-90). The control group of all studies received standard hydration defined as one ml/kg/hr of isotonic saline solution 12 hours prior until 12-24 hours after the procedure. One study included only patients undergoing angiography, while another study only involved patients undergoing PCI. The two others included those undergoing either angiography or PCI. Patients with diabetes were included in all studies except one. All studies excluded patients with acute renal failure, end stage renal disease, shock, heart failure and use of nephrotoxic agents. One study excluded patients who were given N-acetylcysteine within the previous 48 hours. All studies utilized hypo-/iso-osmolar, non-ionic contrast media.

Table I. Characteristics of included RCTs

Study (Year)	No. Control/ No. Intervention	Age (years ±SD)	Diabetic (%)	Baseline SCr (mmol/L ± SD)	NAC given	Contrast volume (mL ± SD)	Hydration & timing	TMZ dose	Timing of TMZ	Timing of SCr determination (hrs. post-CA/PCI)
Onbasili *et al.* (2007)	42/40	60.49 ± 10.51	56.1	113.41 ± 18.01	No	232.68	1cc/kg/hr 12 hrs. prior until 12 hrs. after CA	20mg PO 3x/day	48 hrs. prior until 24 hrs. after CA	24, 48
Rahman *et al.* (2012)	200/200	56.51 ± 10.36	0	123.18 ± 20.75	No	96.40 ± 4.94	1cc/kg/hr 12 hrs. prior until 12 hrs. after CA	35mg PO 2x/day	48 hrs. prior until 48 hrs. after CA	24, 48
Liu *et al.* (2015)	70/62	58.63 ± 10.93	60.6	105.43 ± 21.59	No	122.16 ± 33.06	1-1.5cc/kg/hr 3-12 hrs. prior until 12 hrs. after CA	20mg PO 3x/day	48 hrs. prior until 24 hrs. after CA	48, 72
Shehata *et al.* (2014)	50/50	58.5 ± 5.5	100	176.60 ± 39.74	Yes	275 ± 12.5	1cc/kg/hr 12 hrs. prior until 24 hrs. after PCI	35mg PO 2x/day	48 hrs. prior until 24 hrs. after PCI	72

*CA, coronary angiography; NAC, N-acetylcysteine; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SCr, serum creatinine; TMZ, trimetazidine

Figure 2. Summary of risk of bias assessment of included RCTs

Primary outcome

Pooled results for incidence of CIN are illustrated in Figure 3. In the TMZ plus standard therapy group, 20 of the 352 (5.6%) participants developed CIN compared to 63 out of 362 (17%) who received standard therapy. The TMZ group was significantly less associated with CIN compared to control (RR: 0.33, 95% confidence interval (CI): 020-0.53; $p<.00001$). The absolute risk reduction was 11.4%, with a computed NNT of nine in order to prevent one episode of CIN.

Secondary outcome

The original protocol aimed to synthesize data on dialysis-requiring CIN; however, no incidence of such was reported in any of the studies.

Post-hoc analyses

The authors conducted sensitivity analyses to determine if the pooled estimate of treatment effect would differ if we excluded 1) the subgroup with more severe renal dysfunction at baseline 2) the studies which did not complete 72 hours of monitoring of SCr.

The study by Shehata et al.[23] included patients with relatively more severe renal dysfunction at baseline compared to the other three studies. As demonstrated in Figure 4, there was still a significant difference between treatment groups, favoring the addition of TMZ (RR: 0.30; 95% CI: 0.17-0.53, $p<0.0001$). The magnitude of effect for the subgroup is slightly greater than the pooled estimate, and even more so when compared to the findings of Shehata et al. with a RR of 0.43.

Liu et al.[25] and Shehata[23] observed for CIN up to 72 hours after exposure to contrast, noting the risk ratio for these studies (RR: 0.42, 95% CI 0.22-0.90, $p = 0.008$) is slightly higher than the overall pooled estimate (Figure 5).

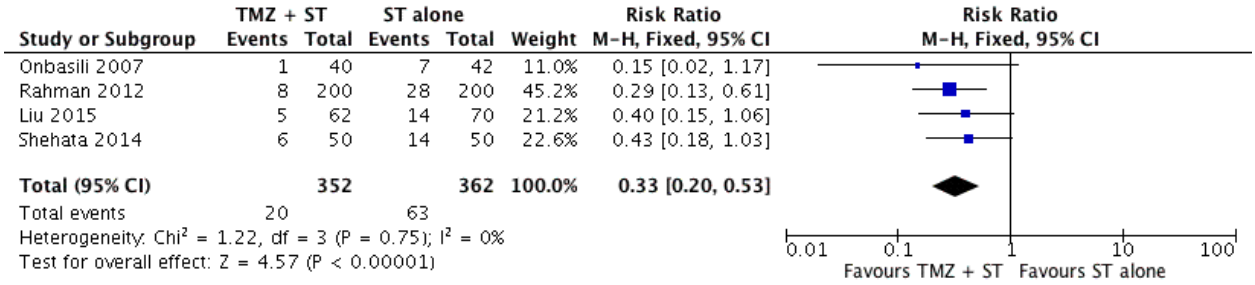

Figure 3. Forest plot showing the risk ratio for contrast-induced nephropathy (CIN) in patients given trimetazidine plus standard therapy versus standard therapy alone. TMZ, Trimetazidine; ST, Standard therapy (Hydration +/- NAC); CI, confidence interval.

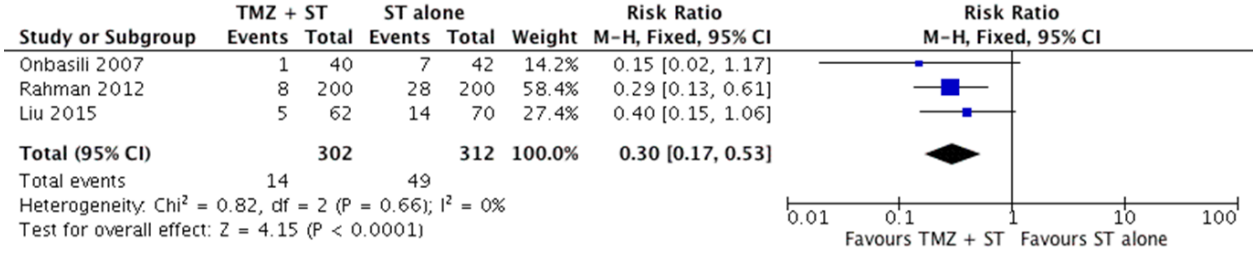

Figure 4. Forest plot showing risk ratio for contrast-induced nephropathy (CIN) in patients given trimetazidine plus standard therapy versus standard therapy alone after excluding the subgroup with more severe renal impairment at baseline. TMZ, Trimetazidine; ST, Standard therapy (Hydration +/- NAC); CI, confidence interval.

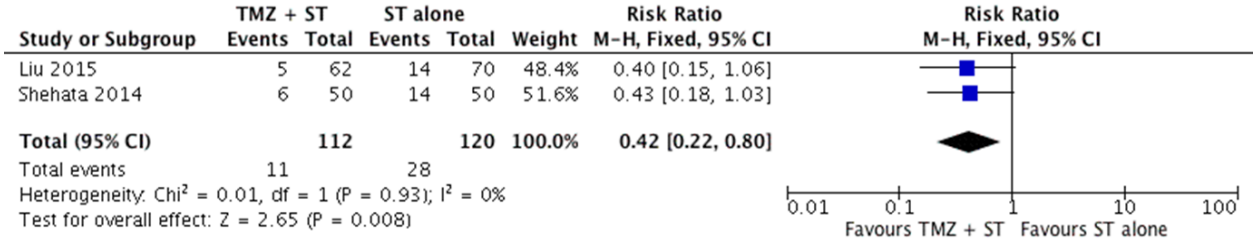

Figure 5. Forest plot showing the risk ratio for contrast-induced nephropathy (CIN) in patients given trimetazidine plus standard therapy versus standard therapy alone after only including studies which observed up to 72 hours after contrast exposure. TMZ, Trimetazidine; ST, Standard therapy (Hydration +/- NAC); CI, confidence interval.

Discussion

Contrast-induced nephropathy (CIN) is a serious complication which needs to be addressed, especially since dialysis requiring CIN confers a very poor prognosis.[9] Even without needing dialysis, occurrence of CIN is still associated with significant morbidity and mortality[6,8] The results of our meta-analysis show that compared to standard hydration ± NAC alone, addition of oral TMZ is associated with a significant decrease in the incidence of CIN after coronary angiography among at-risk patients. The number needed to treat was notably low, with only nine patients needed to be treated with TMZ to prevent the incidence of CIN. However, we were not able to assess its effects in preventing dialysis-requiring CIN because no data were available in the studies.

Our findings affirm the result of the meta-analysis by Nadkarni which showed a similar magnitude of risk reduction of 11%.[24] Inclusion of the study by Liu, which included 132 patients, into the analysis further provided consistency to the evidence for the benefit of trimetazidine in the prevention of CIN.[25]

As of this writing, volume expansion by hydration is the only pharmacological intervention recommended with a high quality of evidence for the prevention of CIN.[3,27,28] The evidence for N-acetylcysteine, on the other hand, is so far inconclusive due conflicting results from various studies[29] With the collective evidence from the RCTs we have obtained, we found that TMZ, an oral anti-ischemic medication with a favorable safety profile, is efficacious in preventing CIN after coronary angiography.

The RCTs included in this analysis enrolled patients with increased risk of CIN due to mild to moderate renal dysfunction with or without diabetes mellitus, but all similarly employed guideline-based volume expansion and used nonionic hypo- to iso-osmolar contrast media. TMZ was administered orally, with a dose of either 20 mg three times a day[21,25] or 35 mg twice a day[22,23], given peri-procedurally for three days. Despite some methodological differences in the included studies, individual study results consistently favor the TMZ group (I^2 = 0%).

Total contrast volume use varied from study to study, with the group of Shehata et al.[23] in particular employing

the highest volume (275 mL) of contrast per procedure, since patients from that group underwent percutaneous coronary intervention together with angiography.

Of note, patients included in the study of Shehata et al. were patients at higher risk of CIN (all diabetic, higher baseline SCr, higher volume of contrast used). We performed a post-hoc analysis to compare the risk ratio of the patients with lower baseline SCr to those with higher baseline SCR and found a slightly lower renoprotective of TMZ for the former. This may or may not imply that TMZ may be less beneficial for those with higher baseline Scr due to the presence of confounding factors. These findings should be further investigated in future studies to better ascertain this effect.

In addition, while an increase in SCr by >0.5mg/dL or >25% from baseline was uniformly used as the definition of CIN, two RCTs measured only up to 48 hours after angiography[21,22], potentially missing a subset of patients that may present with CIN by the 72nd hour. Thus, the incidence of CIN and in turn the effect of TMZ might be under or overestimated. Indeed, the incidence of CIN was lower in the group in which observation was done only for 48 hours (eight percent) compared to those who observed for up to 72 hours (16%), which might explain the lower risk ratio for the former (RR: 0.26, 95% CI: 0.13-0.53) compared to the latter (RR: 0.42; 95% CI: 0.22-0.80).

Dropouts occurred in only one study[25], on which we performed a sensitivity analysis that revealed the results to be robust. While most of the RCTs showed only a trend favoring TMZ (Figure 3), the pooled effect showed a significant decrease in CIN with a relative risk of 0.33 (95% CI 0.20 – 0.53). The particularly wide confidence interval in the study of Onbasili et al.[21] may be due to its small sample size and low incidence of observed outcome. While we also aimed to investigate for the incidence of dialysis-requiring CIN with and without TMZ, none of the included RCTs reported such outcome. This may be due to both the small sample size of the RCTs and the low incidence of dialysis-requiring CIN, showing that a much larger population must be investigated to observe such outcome.

Only one study added another intervention-N-acetylcysteine on top of standard hydration[23] Although this might be seen as a potential confounder, both the treatment group and control group received NAC. Whether or not there was a synergistic effect between NAC and TMZ remains to be seen; a study comparing TMZ alone and TMZ combined with NAC may be necessary. No data was available whether patients were receiving statins, but patients taking any nephrotoxic medications were excluded.

The positive findings we have obtained for TMZ in the prevention of CIN are particularly encouraging given its widespread availability, ease in administration, and safety profile. Many patients who are to undergo coronary procedures might in fact be already on TMZ due to its anti-anginal properties. For the rest of patients, evidence from this review shows that only a short treatment duration is necessary (three to four days) for CIN prevention. Its relatively low cost and oral route of administration make it an acceptable intervention to many patients. Use of TMZ was found to be safe across all studies included, with no attributable adverse events noted.

There are some limitations in our meta-analysis that should be considered. We were unable to analyze and compare CIN risk among non-diabetic versus diabetic patients because separate data on each group was not available in two studies[21,25] Our study population included only patients with a serum creatinine between 83.84-216.34; thus, we were unable to analyze data for those with more severe reductions in creatinine clearance. The current available data is also still insufficient to draw conclusions as to which populations of patients draw the greatest benefit from administration of TMZ in terms of CIN prevention.

Conclusion

Our meta-analysis affirms the findings of previous studies and strengthens the conclusion that TMZ is a safe and effective addition to the strategies employed to prevent CIN. Larger trials may be needed to assess for side-effects and its effect on outcomes such as dialysis-requiring CIN and mortality. We recommend for physicians to consider adding oral TMZ as part of the therapeutic strategy to prevent CIN after coronary angiography or percutaneous coronary intervention among at-risk patients.

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Appendix 1. Risk of bias assessment for individual studies

Liu et al. (2015)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	This study was a prospective, randomized and controlled clinical trial. Patients were randomly allocated into control group (n=75) and TMZ group (n=75).
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias)	Unclear risk	No mention of blinding (but outcome not affected)
Blinding of outcome assessment (detection bias)	Low risk	Clinicians who were responsible for collecting information during follow-up were blind to grouping in this study.
Incomplete outcome data (attrition bias)	Low risk	Complete laboratory tests were not available in 8 patients (control group: n=3, TMZ group: n=5) Results robust with sensitivity analysis.
Selective reporting (reporting bias)	Low risk	There were another 4 patients of TMZ group withdrawing from this study for refusing to use TMZ before PCI; and one patient in TMZ group without receiving coronary angiography due to other reasons. The 18 patients mentioned above were excluded from the final analysis. However, due to nature of intervention (simple to follow and supervised in a hospital setting), virtually very low risk of problems with compliance
Other bias	Low risk	

Onbasili et al. (2007)

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to two groups: TMZ (n=40) and control (n=42).
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias)	Low risk	This study was a prospective double-blind, randomized, controlled trial.
Blinding of outcome assessment (detection bias)	Low risk	This study was a prospective double-blind, randomized, controlled trial.
Incomplete outcome data (attrition bias)	Low risk	No dropouts in the study
Selective reporting (reporting bias)	Low risk	All patients at the start of the trial were accounted for in the results.
Other bias	Low risk	

Rahman et al. (2012)

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The patients were randomly assigned to receive either trimetazidine and hydration with normal saline (treated group) or hydration with normal saline only (control group).
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	No mention of blinding
Blinding of outcome assessment (detection bias)	Low risk	No mention of blinding Although nature of treatment outcome unlikely to be affected by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All subjects analyzed in the group to which they were randomized
Other bias	Low risk	

Shehata et al. (2014)

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	After enrollment and before PCI, patients were randomly assigned in 1:1 fashion to either the trimetazidine group or the control group according to a computer-generated random series of numbers. Randomization was performed by block randomization (blocks of 10 patients).
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Physicians participating in the PCI procedures were unaware of block randomization
Blinding of outcome assessment (detection bias)	Low risk	No mention (although will not affect outcome)
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All subjects analyzed in the group to which they were randomized