Systematic Review and Meta-Analysis

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Trimetazidine reduces contrast-induced nephropathy in patients with renal insufficiency undergoing coronary angiography and angioplasty

A systematic review and meta-analysis (PRISMA)

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Abstract

Objectives: This systematic review and meta-analysis assesses the utility of trimetazidine (TMZ) to prevent contrast induced nephropathy (CIN) in patients with renal insufficiency undergoing coronary angiography and angioplasty.

Materials and methods: This meta-analysis was formulated and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search of databases was conducted by 2 researchers independently for clinical trials, comparing hydration plus TMZ vs conventional hydration alone for prevention of CIN through January 2020. All patients had renal insufficiency (defined as GFR $< 89\,ml/minute/1.73\,m^2$) and the outcome of interest was the incidence of contrast induced acute kidney injury. The odds ratio (OR) was estimated with 95% confidence interval (CI). Heterogeneity was reported with the I^2 statistic, using a fixed-effects model, and >50% of I^2 was considered to be statistically significant.

Results: Eleven studies, 1611 patients, met the inclusion/exclusion criteria: 797 patients comprised the TMZ plus hydration group and the remaining 814 patients comprised the control (hydration only) group. Heterogeneity was low $I^2 = 0\%$, $P = .84$, and the heterogeneity of each study was also low. The incidence of CIN in the TMZ plus hydration group was 6.6% (53/797), while the incidence of CIN in the control (hydration only) group was 20% (165/814). Pooled analysis of all studies showed TMZ reduced incidence of CIN compared to saline hydration alone (OR risk 0.30, 95% CI 0.21, 0.42, $P < .0001$).

Conclusion: TMZ added to hydration reduces CIN in renal insufficiency patients undergoing coronary angiography.

Abbreviations: CAG = coronary angiography, CI = confidence interval, CIN = contrast induced nephropathy, eGFR = estimated glomerular filtration rate, OR = odds ratio, PCI = percutaneous coronary intervention, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized control trial, TMZ = Trimetazidine.

Keywords: angioplasty, contrast-induced nephropathy, coronary angiography, renal insufficiency, trimetazidine

1. Introduction

Contrast-induced nephropathy (CIN), also known as contrast induced acute kidney injury, is a serious complication of diagnostic and interventional angiography procedures, especially for higher risk patient populations undergoing coronary angiography (CAG).[1,2] The incidence of CIN ranges from 1.6% to 2.3% in diagnostic interventions, to as high as 50% in high risk patients undergoing coronary intervention. Intra-arterial injections are associated with the highest incidence rate of CIN. Experimental studies suggest that iodinated contrast damages the renal system in several ways including a direct cytotoxic effect on proximal tubular cells, contrast induction of oxygen free radical formation, and increased resistance to renal

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Study is systematic review and meta-analysis, so ethical approval was not necessary.

The authors have no conflicts of interests to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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blood flow. Patients with underlying renal impairment are at an even greater risk for CIN.[3–5]

Trimetazidine (TMZ) is a fatty acid oxidation inhibitor with cardio-protective effects used in some countries as an antianginal medication. It is not food and drug administration approved and not available in the United States. Small studies have shown TMZ reduces the incidence of CIN mainly by counteracting oxygen radicalization and mitigating the inflammatory response.[6–8] Many other promising treatments for preventing CIN have failed to consistently show a benefit over multiple randomized controlled trials.[9] Here we conduct a systematic review and meta-analysis to determine if adding TMZ to standard hydration therapy consistently reduces CIN in patients with renal insufficiency undergoing CAG and angioplasty.

2. Materials and methods

2.1. Data extraction

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses or PRISMA guidelines.[10] A systematic electronic search to identify relevant original studies was performed. The following search terms were used: ["(contrast media)" OR "contrast induced"), "(nephropathy)" OR "(acute kidney injury)", ("hydration" OR "fluid") and "Trimetazidine"]. The search included alternative names and brands that have been implemented for TMZ such as "Trimetazidine Dihydrochloride" or "Idaptan" or "Danval Brand of Trimetazidine Dihydrochloride" or "Vastarel" or "Biopharma Brand of Trimetazidine or "Trimétazidine Irex" or "Irex Brand of Trimetazidine Dihydrochloride" or "Vasartel" in order to further expand the search in the aforementioned database.

2.2. Study selection, inclusion, and exclusion criteria

A search of Medline, Google Scholar, and Wang Fang database was conducted by 2 researchers independently through January 2020. The following inclusion criteria were applied to determine eligibility. Each study must be a randomized control trial (RCT) with at least 1 observation group receiving TMZ in addition to conventional hydration therapy. In addition, each study must have participants with renal insufficiency (defined as glomerular filtration rate (GFR) < 89 ml/minute/1.73 m^2) Also undergoing CAG or angioplasty.

The estimated glomerular filtration rate (eGFR) were measured in 2 ways: eGFR (male) $= 186 \times (Cr/88.40) - 1.154 \times age - 0.203$; and eGFR (female) $= 186 \times (Cr/88.4) - 1.154 \times age - 0.203 \times 0.742$ in μmol/l.

CIN is defined as the impairment of renal function as determined by either a 25% increase in serum creatinine from baseline or a 0.5 mg/dl increase in the absolute value within 48 to 72 hours after intravenous contrast administration. Retrospective and nonrandomized trial studies were omitted. Semi-RCT and studies in which the grouping method of the participants in the experiment was not strictly random were also excluded from the analysis. Additionally, articles of incomplete or erroneous data were not considered. A total of 1030 studies were collected through a preliminary online search. After applying inclusion and exclusion criteria, 1019 studies were removed from the analysis and 11 studies were considered for qualitative synthesis (Fig. 1).[11–22]

2.3. Statistical analysis

All statistical analyses were performed using StatDx software. Pooled results were reported as Odds ratio (OR). The OR was estimated with 95% confidence interval (CI). Heterogeneity was assessed with the I^2 statistic, using a fixed-effects model. P value less than .5 or I^2 greater than 50% was considered as the existence of substantial heterogeneity (statistically significant). Low to moderate risk of bias was evaluated by Cochran tools (Table 1).

3. Results

Eleven clinical trials from 2006 to 2019, comprised of 1611 patients, met our criteria and were included in the study. (Table 2) In all studies, the incidence of CIN in the hydration group alone (isotonic saline was given 3 to 12 hours before CAG or percutaneous coronary intervention (PCI) and up to 12 hours after the operation at a rate of 1 to 1.5 ml/kg/hour) was compared with the hydration plus TMZ group (TMZ was given 20 mg, 3 times a day or 35 mg, twice a day for 72 to 96 hours, starting 48 hours before procedure). The incidence of CIN in the TMZ plus hydration group was 6.6% (53/797), while the incidence of CIN in the control (Hydration only) group was 20% (165/814). There was low heterogeneity: $I^2 = 0\%$, $P = .84$. Addition of TMZ to hydration reduced the incidence of CIN with an OR = 0.30, 95% CI 0.21, 0.42, $P < .000$) compared to standard hydration therapy alone in patients with renal insufficiency undergoing CAG or angioplasty (Figure 2). No potential side effects relevant to TMZ administration were reported in included papers.

3.1. Asian vs non-Asian populations

To explore effects of ethnicity, patients were able to be divided into Asian and non-Asian populations. Heterogeneity in each group of studies was low (Asian group: $I^2 = 0\%$, $P = .57$, and non-Asian group: $I^2 = 0\%$, $P = .87$). Meta-analysis performed separately in each group showed that TMZ added to hydration significantly reduces the incidence of contrast induced nephropathy (CIN), (Asian population: OR 0.30, 95% CI 0.2, 0.44, $P < .0001$, non-Asian: OR 0.30, 95% CI 0.17, 0.56, $P < .0001$) (Figure 3).

3.2. Type of contrast agent

Five studies used iodixanol, 4 studies used iopramide, 1 study used ioversol, and the type of iodinated contrast agent was not reported in 2 studies (Table 1).

Meta-analysis performed separately in 2 group of studies based on type of contrast, including group used iodixanol (isosmolar iodine agent) vs group of studies used low osmolar iodine contrast agent including iopramide and ioversolm. A forest plot, Figure 4, shows that TMZ added to hydration had similar performance in reducing CIN on the various type of contrast agent type (Fig. 4).

4. Discussion

Although CIN risk in healthy patients undergoing intravenous injections for CT scans has likely been over,[23,24] it remains a serious concern in patients receiving intra-arterial injections and especially for patients with underlying renal dysfunction. CAG and percutaneous coronary intervention (PCI) patients with renal

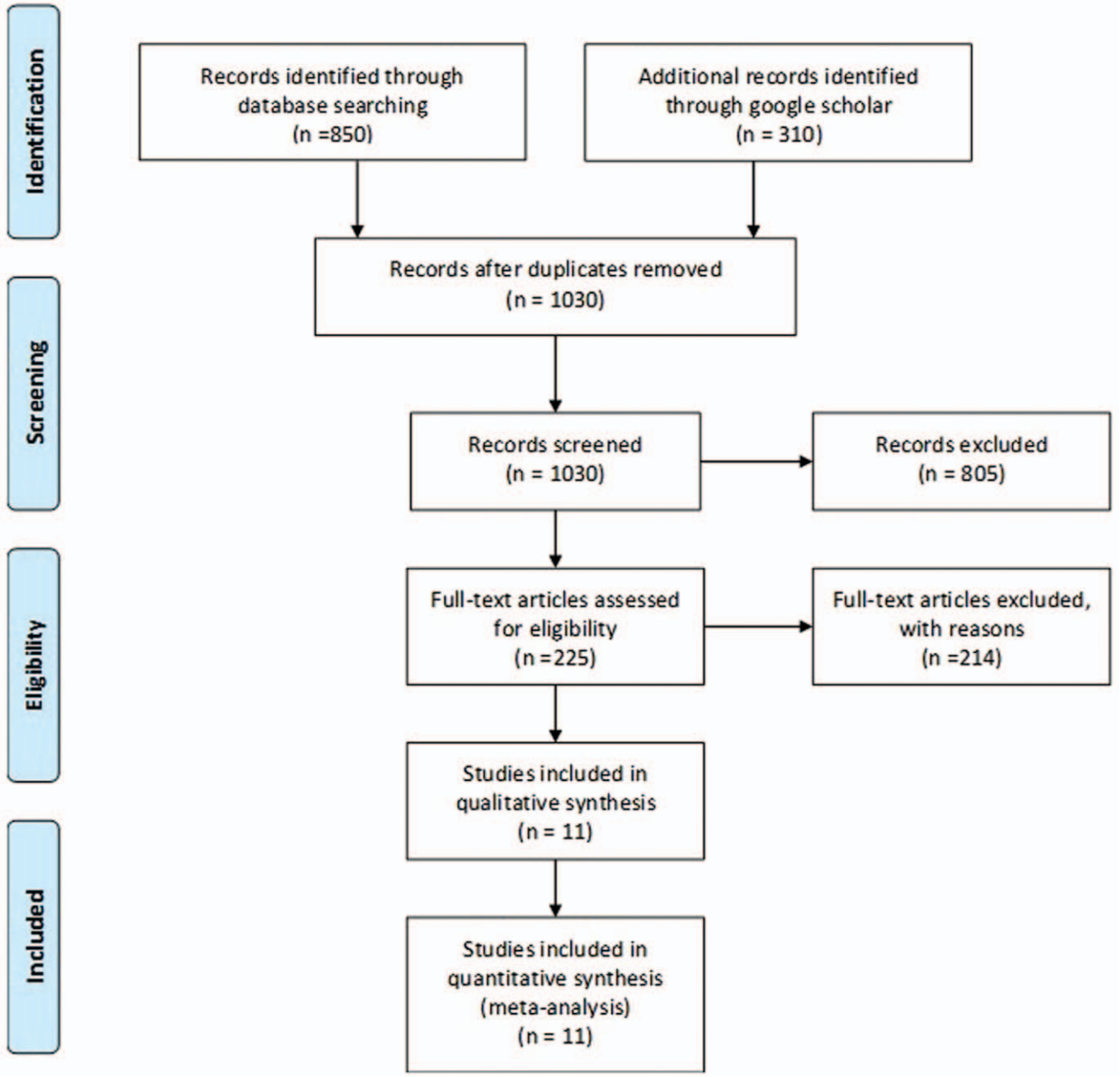

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Table 1

Assessment of methodological quality of included studies.

First author	Year publication	Random allocation	Blind method	Incomplete outcome data	Selective bias of reporting	Other bias	Quality grade
Mirhosseini[11]	2019	20 mg, 3 times a day for 72 h	Double blind	Low	Low	Low	A
Chen[12]	2018	20 mg, 3 times a day for 72 h	Single blind	Low	Low	Low	A
Ye[13]	2017	20 mg, 3 times a day for 72 h	Single blind	Low	Low	Low	A
Ibrahim[14]	2017	35 mg twice daily for 72 h	Single blind	Low	Low	Low	A
Liu[15]	2015	20 mg, 3 times for 96 h	Single blind	Low	Low	Low	A
Huaizhou[16]	2014	20 mg, 3 times for 96 h	Not clear	Low	Low	Low	B
Cheng[17]	2014	20 mg, 3 times for 72 h	Single blind	Low	Low	Low	A
Shehata[18]	2014	35 mg twice daily for 72 h	Single blind	Low	Low	Low	A
Rahman[19]	2012	35 mg twice daily for 96 h	Not Clear	Low	Low	Low	B
Wang[20]	2010	20 mg, 3 times for 96 h	Not clear	Low	Low	Low	B
Onbasili[21]	2006	20 mg 3 times a day for 72 h	Double blind	Low	Low	Low	A

Table 2

Characteristics of studies included in meta-analysis*.

First author	Year publication	Sample #		Groups		Dosage of trimetazidine	Type of contrast	Type of procedure
		TMZ + hydration		hydration				
Mirhosseini[11]	2019	50	50	8%	22%	20 mg, 3 times a day for 72 h	Iodixanol	Coronary angiography
Chen[12]	2018	75	75	6.6%	21.3%	20 mg, 3 times a day for 72 h	Iopramide	PCI
Ye[13]	2017	54	52	9.3%	16.7%	20 mg, 3 times a day for 72 h	Iodixanol	Coronary angiography or PCI
Ibrahim[14]	2017	50	50	10%	26%	35 mg twice daily for 72 h	Iodixanol	Coronary angiography or PCI
Liu[15]	2015	62	70	8%	20%	20 mg, 3 times for 96 h	Iodixanol	Coronary angiography or PCI
Huaizhou[16]	2014	50	50	8%	18%	20 mg, 3 times for 96 h	Not clear	Coronary angiography
Cheng[17]	2014	64	60	3%	16.7%	20 mg, 3 times for 72 h	Ioversol	Coronary angiography or PCI
Shehata[18]	2014	50	50	12%	28%	35 mg twice daily for 72 h	Iopramide	PCI
Rahman[19]	2012	200	200	4%	14%	35 mg twice daily for 96 h	Not clear	PCI
Wang[20]	2010	102	115	3%	18.2%	20 mg, 3 times for 96 h	Iohexol	Coronary angiography
Onbasili[21]	2006	40	42	2.5%	16.6%	20 mg 3 times a day for 72 h	Iopramide	Coronary angiography

* In All Clinical trials included in meta-analysis CIN is defined as the impairment of renal function determined by either a 25% increase in SCr (serum creatinin) from baseline or 0.5 mg/dl (44 mmol/L) increase in absolute value, within 48 to 72 hours of intravenous contrast administration.

PCI = percutaneous coronary intervention.

insufficiency are a particularly high risk group.[11–22] Observational studies demonstrated that the immediate in-hospital and 30-day mortality rates were significantly higher in CIN compared to non-CIN patients (7.1% vs 1.1% and 5% vs 0.7%, respectively). Furthermore, there is a higher incidence of persistent renal function decline in the patients developing CIN.[25–27] Although CIN has defined been defined as either a 25% increase in serum Cr from baseline or a 0.5 mg/dl (44 μmol/L) increase in serum Cr within 48 to 72 hours following iodinated contrast administration, its strong association with CAG/

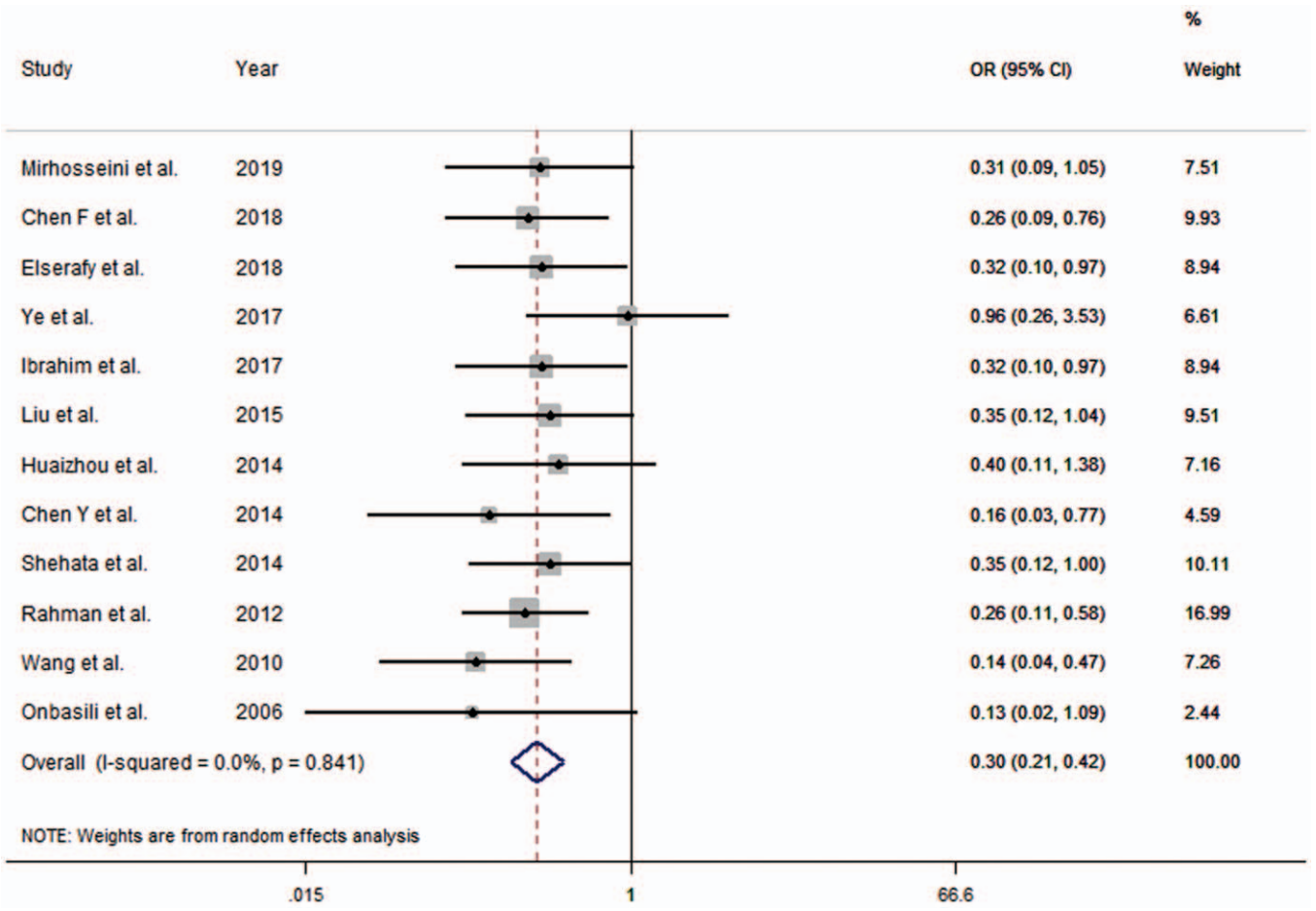

Figure 2. Forest plot of 11 randomized controlled trials showing low heterogeneity between studies: $I^2 = 0\%$, $P = .84$. Overall, trimetazidine added to hydration reduced the incidence of contrast induced nephropathy compared to standard hydration therapy alone in patients with renal insufficiency OR:0.30, 95% confidence interval [CI] 0.21, 0.42, $P < .000$).

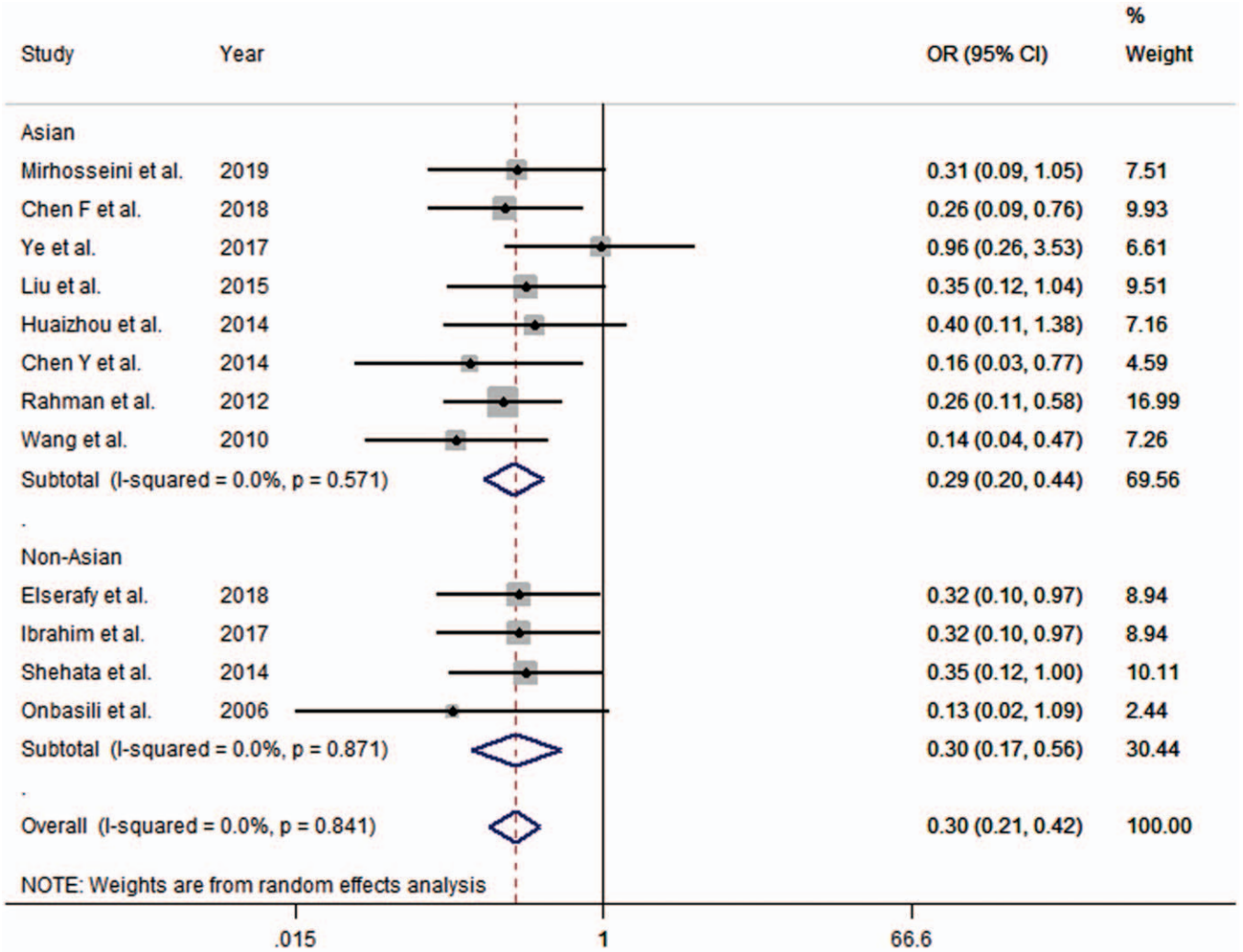

Figure 3. The results of the meta-analysis showed Low heterogeneity on both Asian and non-Asian groups: $I^2 = 0\%$, $P = .57$, $I^2 = 0\%$, $P = .87$ .Meta-analysis from both groups showed that trimetazidine added to hydration significantly reduces the incidence of contrast induced nephropathy, Asian population: OR 0.30, 95% confidence interval [CI] 0.2, 0.44, $P < .000$, non-Asian: OR 0.30, 95% confidence interval [CI] 0.17, 0.56, $P < .000$).

angioplasty raises the possibility of a synergism between the intra-arterial contrast agent injection and other peri-procedural nephrotoxic events occurring in these patients. Regardless of the actual cause of CIN, there has been a concerted effort to identify preventative measures.[9,25–27] But, thus far, only hydration with normal saline has been established as effectively reducing CIN.[28,29] However, this meta-analysis of 11 randomized controlled trials comparing TMZ with hydration to hydration alone shows an impressive protective effect consistently observed with low heterogeneity.

Various studies have investigated other potential medications for the prevention of CIN, but showed inconsistent or non-beneficial results. Such medications include *N*-acetylcysteine, sodium bicarbonate containing intravenous fluid, Vitamin C, Vitamin E, calcium channel blockers, dopamine, and statins.[9,30–36] TMZ is an antiischemic (antianginal) metabolic agent, which improves myocardial glucose utilization through inhibition of fatty acid metabolism. TMZ derives its cytoprotective effects via enhancement of mitochondrial activity which yields a reduction in the release of oxygen-free radicals, a reduction in membrane lipid peroxidation, and inhibition of neutrophil infiltration after ischemia–reperfusion.[37,38] These cytoprotective effects explain why compared to placebo, TMZ was associated with a reduction in weekly angina episodes and improved exercise time to 1 mm ST segment depression.[39] A multicenter study by Fragasso et al, showed that in patients with heart failure of different etiologies, addition of TMZ to conventional optimal therapy can reduce mortality and morbidity.[40]

Pharmacological characteristics of TMZ make it a promising agent for the prevention of CIN. An experiment by Grekasn et al[41] which studied the effects of TMZ on renal ischemia reperfusion injury in animal model, and the results showed that TMZ could reduce malondialdehyde (MDA) levels, indicating reduced lipid peroxidation, which in renal tissue corresponds to less oxygen free radical-induced renal injury. Akgullu et al, have confirmed that TMZ reduces MDA levels in the kidney after exposure to iodinated contrast and increases superoxide dismutase activity for scavenging free radicals.[42]

Since TMZ is not currently approved by the food and drug administration for sale in the USA, a disproportionate number of studies included in this meta-analysis were from Asian. This enabled us to compare the results in Asian vs non-Asian subjects:

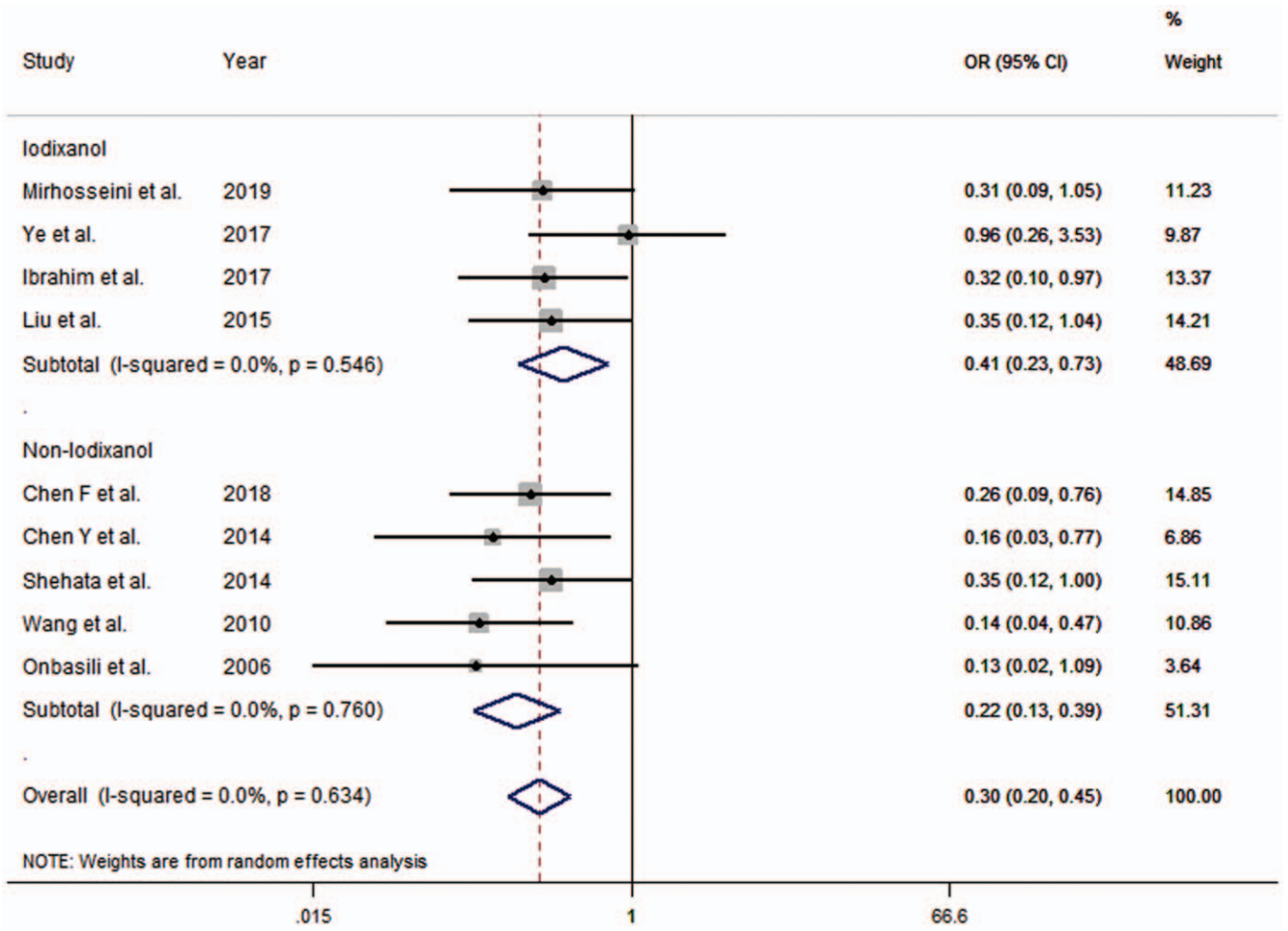

Figure 4. The results of the meta-analysis showed low heterogeneity on both iodixanol and non-iodixanol groups: $I^2 = 0\%$, $P = .55$, $I^2 = 0\%$, $P = .63$. Meta-analysis from both groups showed that Trimetazidine added to hydration significantly reduces the incidence of contrast induced nephropathy,Iodixanol: OR 0.4, 95% confidence interval [CI] 0.22, 0.70, $P < .000$, non-iodixanol: odds ratio 0.22, 95% confidence interval [CI] 0.13, 0.39, $P < .000$).

no difference was identified with a similar 3-fold reduction in OR for developing using TMZ in both groups. Additional benefits of TMZ are its low price and its favorable safety profile has been well established in animal and human studies.[41,42]

Limitations of this meta-analysis include its use only in CAG and coronary interventional procedures with intra-arterial contrast agent injections. Generalization to a benefit with intravenous contrast agent administration such as used in CT scanning is promising but has not been established. Present data is a meta-analysis, using published data of each study selected. This is per se a possible cause of bias. There are differences in methodology between the studies including use in different populations with different doses of TMZ and iodinated contrast. However the consistent observation of a benefit with TMZ for reducing CIN suggests these confounding effects may be minor: Limited number of articles, dosage inconsistencies between studies, unknown population distribution, and indeterminate long term outcomes.

5. Conclusion

Combined data from 11 randomized control trials showed that TMZ added to standard normal saline hydration consistently reduced the incidence of CIN by 3-fold in high risk patients with renal insufficiency undergoing angioplasty or angiography.

Author contributions

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Writing – review & editing: Ashkan Heshmatzadeh Behzadi, Martin R Prince.

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