ORIGINAL ARTICLE

The role of probucol preventing contrast-induced nephropathy in patients undergoing invasive coronary procedures – Systematic review and meta-analysis of randomized controlled trials

Girişimsel koroner işlem uygulanan hastalarda probukolün kontrast madde nefropatisini önlemedeki rolü - Randomize kontrollü çalışmaların sistematik incelemesi ve meta-analizi

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ABSTRACT

Objective: The aim of this meta-analysis was to synthesize the latest evidence on the effect of probucol on the incidence of contrast-induced nephropathy (CIN) in patients undergoing coronary angiography (CAG)/percutaneous coronary intervention (PCI).

Methods: A systematic literature search of PubMed, ScienceDirect, EuropePMC, ProQuest, and Clinicaltrials.gov was performed to retrieve studies that assessed probucol and CIN in CAG/PCI.

Results: Four studies that compared probucol with hydration alone, comprising 1270 subjects, were identified and analyzed. There was no significant difference between probucol and control groups in the baseline level of creatinine and at 48 hours; however, a significant difference was observed at 72 hours (mean difference: -3.87 μmol/L; 95% confidence interval [CI]: -6.58, -1.15; p=0.005). The meta-analysis indicated that probucol did not reduce the CIN incidence (odds ratio [OR]: 0.46; 95% CI: 0.20, 1.08; p=0.08). After performing a leave-one-out sensitivity analysis, removal of a study resulted in a lower risk of CIN (OR: 0.33; 95% CI: 0.19, 0.56; p<0.001). Probucol did not reduce the CIN incidence in a pooled adjusted effect estimate (OR: 0.75; 95% CI: 0.15, 3.87; p=0.73). There was no significant difference in the rate of major adverse events between the 2 groups (OR: 0.39; 95% CI: 0.05, 3.05; p=0.37). Funnel plot results were asymmetrical, indicating possible publication bias. Grading of Recommendations, Assessment, Development and Evaluations qualification demonstrated a low and very low certainty of evidence in unadjusted and adjusted effect estimates, respectively.

Conclusion: Probucol did not reduce the incidence of CIN; however, due to the low certainty of evidence, further study is required for a definite conclusion. Although the p value was not significant, the confidence interval showed a nonsignificant trend toward benefit. However, this trend might have been due to publication bias.

ÖZET

Amaç: Bu meta-analizin amacı, koroner anjiyografi (KAG) / perkütan koroner girişim (PKG) uygulanan hastalarda, probukolün kontrast madde nefropatisi (KMN) insidansı üzerindeki etkisine ilişkin en son bulguları bir araya getirmektir.

Yöntemler: KAG/PKG uygulanan hastalarda probukol ve KMN'ni değerlendiren çalışmaların derlenmesine yönelik olarak PubMed, ScienceDirect, EuropePMC, ProQuest ve Clinical-trials.gov'da sistematik bir literatür taraması yapılmıştır.

Bulgular: Probukolü sadece hidrasyonla karşılaştıran ve 1270 denekten oluşan dört çalışma saptanarak analiz edildi. Temel kreatinin seviyesinde ve 48 saatte probukol ve kontrol grupları arasında anlamlı bir fark olmadığı; ancak 72 saatte önemli bir fark olduğu görülmüştür (ortalama fark: -3.87 μmol/L; %95 güven aralığı [GA]: -6.58, -1.15; p=0.005). Meta-analizde, probukolün KMN insidansını azaltmadığı saptandı (olasılık oranı [OR]: 0.46; %95 GA: 0.20, 1.08; p=0.08). Çalışmalardan birini dışarıda bırakan bir duyarlılık analizinin yapılmasından sonra, daha düşük bir KMN riski sonucunu elde edildi (OR: 0.33; %95 GA: 0.19, 0.56; p<0.001). Probucol, havuzlanmış düzeltilmiş bir etki tahmininde CIN insidansını azaltmamıştır (OR: 0.75; %95 GA: 0.15, 3.87; p=0.73). İki grup arasında majör istenmeyen olayların oranında anlamlı bir fark yoktu (OR: 0.39; %95 GA: 0.05, 3.05; p=0.37). Huni saçılım grafiği sonuçlarının asimetrik olarak ortaya çıkması olası yayın yanlılığını göstermektedir. Öneri, Değerlendirme, Geliştirme ve Değerlendirme yeterliliğinin derecelendirilmesi, sırasıyla düzeltilmemiş ve düzeltilmiş etki tahminlerinde düşük ve çok düşük kesinlik göstermiştir.

Sonuç: Probukol, KMN insidansını azaltmamıştır; ancak kanıt kesinliğinin zayıf olmasından dolayı daha kesin bir sonuç elde edilmesi için daha fazla çalışmanın gerçekleştirilmesi gerekmektedir. P değeri istatistiksel olarak anlamlı olmamasına karşın, güven aralığı faydaya doğru anlamlı olmayan bir eğilim göstermiştir. Ancak, bu eğilimin yayın önyargısından kaynaklanması olasıdır.

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Contrast-induced nephropathy (CIN) may occur in up to 14% of patients who undergo coronary angiography (CAG) or percutaneous coronary intervention (PCI), and the ratio may be greater in patients with renal dysfunction.[1–3] There are various definitions for CIN; one of the most widely used is that of the European Society of Urogenital Radiology: increase of the serum creatinine level ≥0.5 mg/dL (44.2 mmol/L) or >25% of the baseline value 48–72 hours after contrast media (CM) administration.[4] CIN is the third leading cause of acute kidney injury in hospitalized patients[5] and is associated with increased morbidity and mortality, including in patients undergoing PCI.[6] Several efforts have attempted to reduce the risk of CIN,[7,8] however, most pharmacological treatment has failed.[9] Adequate hydration remains the cornerstone of CIN prevention.

Probucol is a potent antioxidant medication that exerts antioxidative stress and anti-inflammatory properties; it has been associated with improved renal vascular endothelial function.[10–12] While the definitive pathophysiology of CIN is yet to be fully elucidated it is thought to be mediated by oxidative stress, renal vasoconstriction, and tubular cell damage,[13] and improvement in endothelial function along with anti-oxidative-inflammatory properties may act against CIN pathogenesis. The role of probucol is still controversial. A 2019 study has shown that it was not beneficial, which is consistent with some earlier reports.[14,15] The aim of this systematic review and meta-analysis was to synthesize the latest evidence available regarding the effect of probucol on the incidence of CIN in patients undergoing CAG/PCI.

METHODS

Search strategy

A systematic literature search was performed for studies that assessed probucol and CIN in CAG/PCI patients with the keywords "probucol," "contrast-induced nephropathy," and its synonym through December 2019 in PubMed, ScienceDirect, EuropePMC, ProQuest, Clinicaltrials.gov, as well as a hand-search of articles cited by other studies. Duplicates were removed and the records were systematically evaluated based on inclusion and exclusion criteria. The initial search was performed independently by 2 researchers and discrepancies were resolved by discussion. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the literature search strategy of studies is shown in Figure 1.

Abbreviations:

AMI	*Acute myocardial infarction*
CAG	*Coronary angiography*
CI	*Confidence interval*
CIN	*Contrast-induced nephropathy*
CM	*Contrast media*
HDL	*High-density lipoprotein*
I2	*Inconsistency index*
OR	*Odds ratio*
PCI	*Percutaneous coronary intervention*
RCT	*Randomized controlled trial*

Study selection

The inclusion criteria for this systematic review were studies that assessed probucol and CIN in patients undergoing CAG and/or PCI. All related clinical research/original articles were included, and case reports, letters to the editor, commentaries, and review articles were excluded.

Data extraction and quality assessment

Two independent authors performed the data extraction and quality assessment using a standardized form that includes authors, year of publication, study design, funding, subject characteristics, CAG/PCI procedure, sample size, probucol protocol details, hydration protocol details, number of males, mean/median age, CIN definition, CIN incidence, major adverse events, and funding of each studies. The Cochrane risk-of-bias tool for randomized trials was used to assess the risk of bias in the included studies.

Statistical analysis

Review Manager (RevMan) Version 5.3. (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA Version 16.0 (StataCorp LP, College Station, TX, USA) were used to perform the meta-analysis. The Mantel-Haenszel method was used to calculate odds ratios (ORs) and generic inverse-variance to pool-adjusted OR with random-effects model regardless of heterogeneity. The OR is reported along with a 95% confidence interval (CI). To assess inter-study heterogeneity, an inconsistency index (I2) test, which ranges from 0–100%, was performed. A value of >50% or $p<0.10$ indicated statistically significant heterogeneity. Publication bias was assessed qualitatively using funnel-plot analysis. The small-study effect was assessed quantitatively using a regression-based test (Harbord test) for binary outcomes. It should be noted that the analyses for publication bias and small-study effect were less reliable when there were fewer than 10 stud-

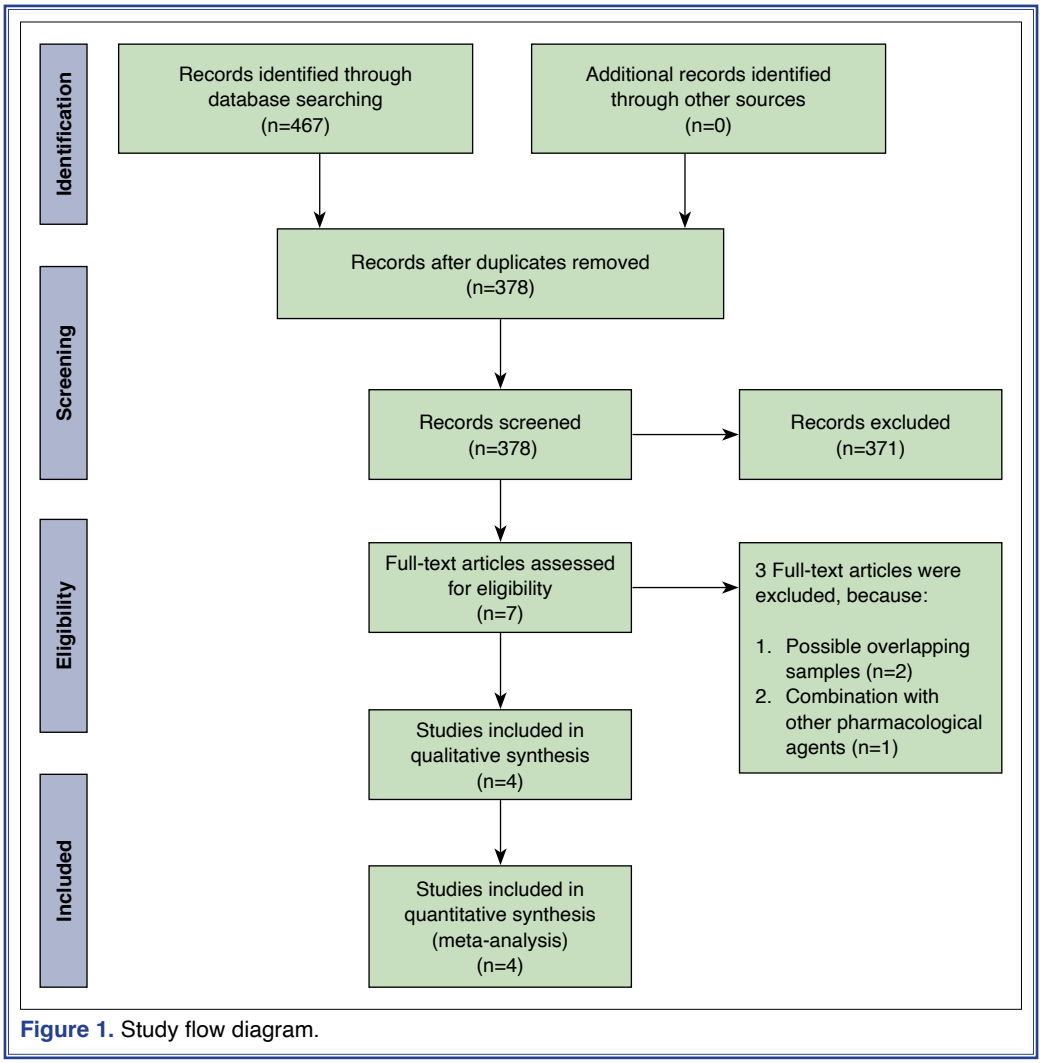

Figure 1. Study flow diagram.

ies. P values in this study were 2-tailed and a value of <0.05 indicated statistical significance. GRADEpro GDT: GRADEpro Guideline Development Tool software (McMaster University, Hamilton, Ontario, Canada; developed by Evidence Prime, Inc., Hamilton, Ontario, Canada) was used to assess the certainty of evidence.

RESULTS

A total of 467 records were obtained in the initial search, and 378 remained once duplicates were eliminated. After title and abstract screening, 371 records were excluded. After assessing the final 7 full texts for eligibility, 3 studies were omitted due to possibly overlapping samples (n=2), and the use of probucol in combination with other pharmacological agents (n=1). In all, 4 studies were included in the qualitative synthesis and meta-analysis (Fig. 1). All 4 studies were randomized controlled trials (RCTs). There were a total of 1270 subjects in the 4 studies[14–17] (Table 1). The control groups were hydration-only groups (no placebo).

Characteristics of the studies and patients

Three studies were a single-blind RCT, and 1 was a double-blind RCT. All of the studies were conducted in China: 3 studies were from the city of Tianjin, and 1 study was from Shangqiu. Elective surgery was the focus of 3 studies, and 1 examined primary/urgent angioplasty. Both the probucol and control groups received standard hydration. Probucol was administered at a dose of 500 mg twice daily until 3 days after the procedure. Two studies initiated probucol 1 day before the procedure and 1 study started 3 days before the procedure. The angioplasty study administered

Table 1. Characteristics of studies included in the systematic review

Study	Design	Location	Sample size	Probucol protocol	Hydration protocol	Definition of CIN	Incidence of CIN	Inclusion criteria	Age (years)	Male (%)	Baseline CCr	Funding
Wang 2019	Double-blind RCT	The First People's Hospital of Shangqiu (2017-2018)	220 (110/110)	500 mg twice daily at 1 day before and 3 days after procedure	IV NaCl 0.9% 1.0 mL per kg of body weight per hour from 12 hours before to 12 hours after procedure	Increase in SCr by ≥0.5 mg/dL (≥44.2 mmol/L) or ≥25% from the baseline value within 48-72 hours after CM exposure	16 (7.27%)	Elective PCI	63.42±10.69 vs 60.79±11.01	61.8 vs 58.2	87.65±26.34 vs 85.16±27.10 <60 mL/min (Unclear)	None
Fu 2017	Single-blind RCT	Tianjin Chest Hospital, Tianjin First Central Hospital, Tianjin Fourth Central Hospital, and Teda International Cardiovascular Hospital (2014-2016)	641 (321/320)	500 mg twice daily at 1 day before and 3 days after procedure	IV NaCl 0.9% 1.0 mL per kg of body weight per hour from 12 hours before to 12 hours after procedure	Increase in SCr by ≥0.5 mg/dL (≥44.2 mmol/L) or ≥25% from the baseline value within 72 hours after CM exposure	48 (7.49%)	Elective PCI	60.33±11.69 vs 61.88±12.35	57.3 vs 59.1	78.23±15.99 vs 78.21±16.41 <60 ml/min (21.9 vs 20%)	Tianjin Municipal Health and Family Planning Commission
Yin 2013	Single-blind RCT	Second Hospital of Tianjin Medical University (2009-2010)	204	1000 mg orally before primary or urgent angioplasty and 500 mg twice daily for 3 days after procedure	IV NaCl 0.9% 1.0 mL per kg of body weight per hour for 24 hours after procedure	Increase in SCr by ≥0.5 mg/dL (≥44.2 mmol/L) or ≥25% from the baseline value within 72 hours after CM exposure (Secondary Endpoint)	27 (13.2%)	Primary or Urgent Angioplasty STEMI (68.6%) NSTEMI (31.4%)	65.1±10.5 vs 65.4±12.5	69.8 vs 68.5	82.9±27.6 vs 81.1±27.7 <60 ml/min (18.8 vs 23.2%)	N/A
Li 2009	Single-blind RCT	Second Hospital of Tianjin Medical University (2007-2008)	205 (102/103)	500 mg orally twice daily for 3 days before and after the procedure	IV NaCl 0.9% 1.0 mL per kg of body weight per hour for 12 hours after procedure	Increase in SCr by ≥0.5 mg/dL (≥44.2 mmol/L) or ≥25% from the baseline value within 72 hours after CM exposure	23 (11.2%)	CAG/PCI (unknown percentage)	62±11 vs 63±11	49 vs 64	75±27 vs 76±25 <60 ml/min (29 vs 27%)	N/A

CAG: Coronary angiography; CCr: Creatinine clearance; CIN: Contrast-induced nephropathy; CM: Contrast media; IV: Intravenous; N/A: Not available; NaCl: Sodium chloride; NSTEMI: Non-ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; RCT: Randomized controlled trial; SCr: Serum creatinine; STEMI: ST-elevation myocardial infarction.

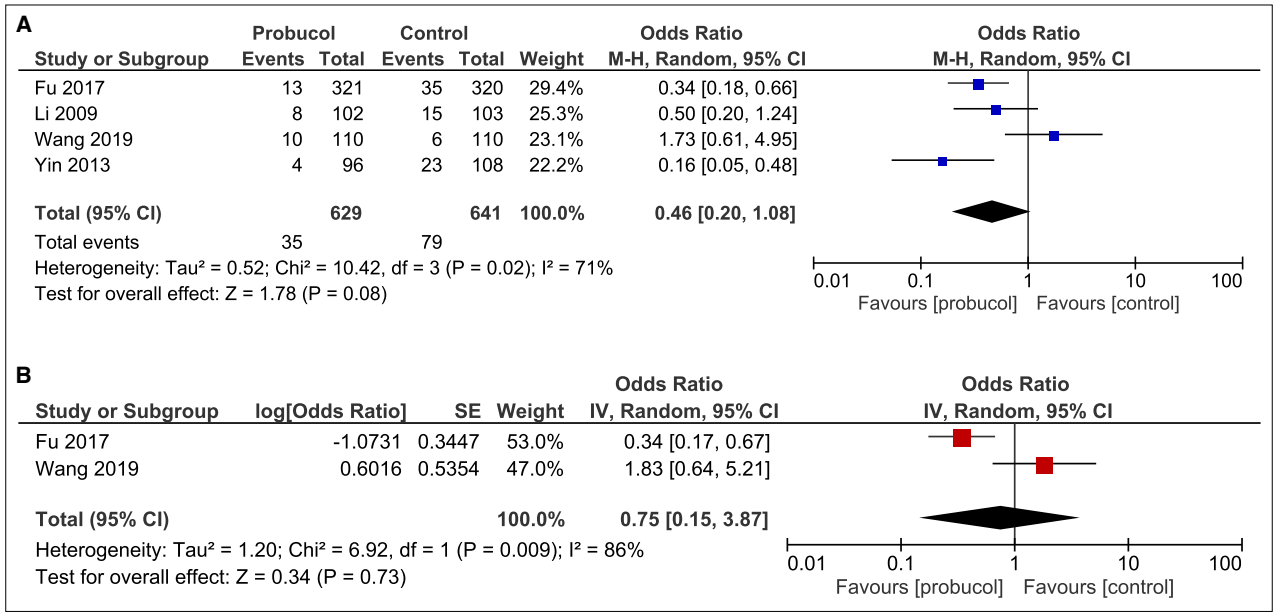

Figure 2. Probucol and contrast-induced nephropathy. Forest plots demonstrating **(A)** pooled odds ratio and **(B)** adjusted odds ratio.

1000 mg before the procedure. The control groups received a standard hydration protocol only. The definition used for CIN was an increase in serum creatinine of ≥0.5 mg/dL (≥44.2 mmol/L) or ≥25% from the baseline value within 48–72 hours after CM exposure. The total incidence of CIN was 8.98%.

Serum creatinine

A meta-analysis performed for the Fu et al. and Wang et al. studies revealed no significant difference in the baseline level of creatinine (mean difference: -0.37 μmol/L, [95% CI: -2.54, 1.80], p=0.74; I^2: 0%, p=0.74) and 48 hours (mean difference: -2.48 μmol/L, [95% CI: -5.47, 0.50], p=0.10; I^2: 0%, p=0.10) between the probucol and control groups. A significant difference was observed 72 hours after contrast administration. The serum creatinine level was lower in the probucol group (mean difference: -3.87 μmol/L, [95% CI: -6.58, -1.15], p=0.005; I^2: 0%, p=0.50). Li et al. reported results in mg/dL rather than not μmol/L, and they found that there was a significant difference in the creatinine level at 48 hours but not 72 hours between the probucol and control groups. Yin et al. provided a baseline serum creatinine for both groups, but they did not provide follow-up serum creatinine measurements according to probucol and control groups.

Contrast-induced nephropathy

The meta-analysis showed that probucol did not reduce the incidence of CIN (OR: 0.46, [95% CI: 0.20, 1.08], p=0.08; I^2: 71%, p=0.02) (Fig. 2a). After performing a leave-one-out sensitivity analysis, removal of the Wang et al. study resulted in a lower risk of CIN (OR: 0.33, [95% CI: 0.19, 0.56], p<0.001; I^2: 19%, p=0.29), denoting weakness in the analysis. Probucol was not associated with a reduction of CIN in the pooled adjusted-effect estimate (OR: 0.75, [95% CI: 0.15, 3.87], p=0.73; I^2: 86%, p=0.009) (Fig. 2b).

Major adverse events

Fu et al. and Wang et al. reported major adverse events in their study. However, the meta-analysis revealed no significant difference in the rate of major adverse events between the probucol and control groups (OR: 0.39, [95% CI: 0.05, 3.05], p=0.37; I^2: 52%, p=0.15).

Publication bias

One of the most concerning risks of bias for individual studies is a non-double-blind format. Only 1 study had a double-blind design (Fig. 3a). All of the studies were from China, and 3 were from Tianjin (Table 1). Funnel plot analysis was qualitatively asymmetrical, indicating a risk of publication bias (Fig. 3b). A regression-based Harbord's test showed that the results of probucol on CIN were not statistically significant for small-study effects (p=0.401) (Fig. 3c).

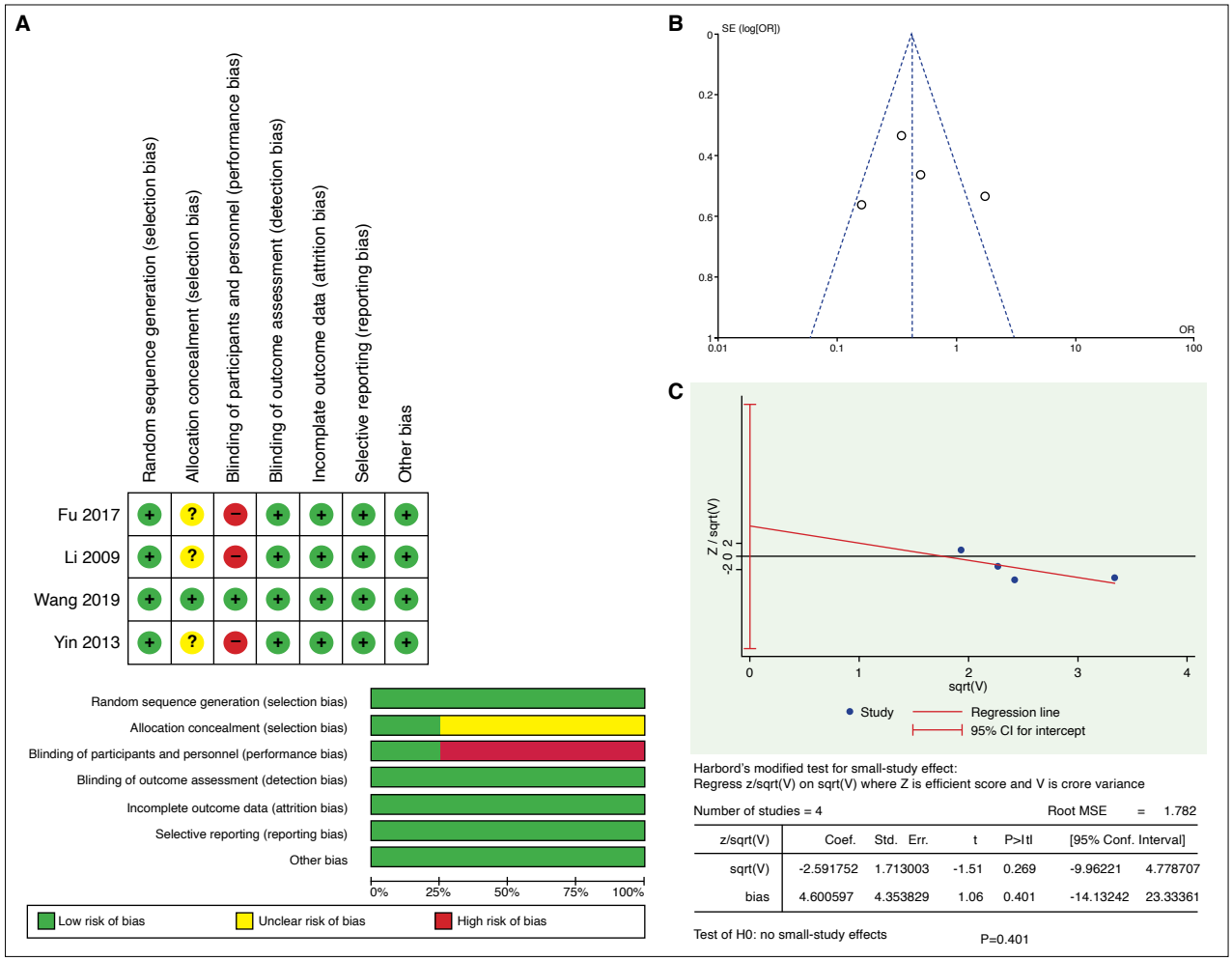

Figure 3. **(A)** Cochrane risk of bias assessment, **(B)** asymmetrical funnel-plot analysis, **(C)** regression-based Harbord's test indicating no statistically significant small-study effect.

GRADE qualification

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) qualification revealed that probucol was associated with a low certainty for its effect on CIN in unadjusted OR and a very low certainty of evidence in the adjusted model (Table 2). The high risk of publication bias along with inadequate blinding and high heterogeneity downgrade the level of evidence.

DISCUSSION

This meta-analysis revealed that probucol did not reduce the incidence of CIN, however, due to the low certainty of evidence, further study is needed to make a definitive conclusion. Although the p-value was not significant, the confidence interval showed a non-significant trend toward a benefit. However, the trend observed might be due to publication bias. The certainty of the evidence was low, and the latest RCT that had the lowest risk of bias demonstrated a non-significant lessening effect on CIN. It is interesting that the strongest benefit was observed in patients undergoing primary/urgent angioplasty due to acute myocardial infarction (AMI), indicating a possible benefit in this subset of patients.

A previous meta-analysis found that probucol reduced CIN in patients undergoing coronary angiography or PCI with 0% heterogeneity using I2 analysis.[18] However, with the addition of the recent Wang et al.[14] study, which has the lowest risk of bias, heterogeneity rose to 71% in our study. The Wang et al.[14] research was the only study that had an OR of >1 in the forest plot. Along with the asymmetrical fun-

Table 2. GRADE qualification of the meta-analysis

Certainty assessment							No of patients		Effect	Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probucol	Placebo	Odds Ratio (95% CI)	
Unadjusted OR for Probucol on CIN										
4	Randomised trials	Serious[a]	Serious[b]	Not serious	Not serious	Publication bias strongly suspected strong association[c]	35/629 (5.6%)	79/641 (12.3%)	OR 0.46 (0.20 to 1.08)	⊕⊕◯◯ LOW
Adjusted OR for Probucol on CIN										
2	Randomised trials	Serious[a]	Serious[b]	Not serious	Not serious	Publication bias strongly suspected[c]	23/431 (5.3%)	41/430 (9.5%)	OR 0.75 (0.15 to 3.87)	⊕◯◯◯ VERY LOW

CI: Confidence interval; CIN: Contrast-induced Nephropathy; OR: Odds ratio
Explanations: [a]Inadequate blinding of the studies; [b]High-heterogeneity with one unexplainable deviation; [c]Asymmetrical funnel plot.

nel plot of the current meta-analysis, the presence of publication bias is likely. It should be noted that funnel-plot analysis is reliable with >10 studies; this study demonstrated the possibility of publication bias in the current literature.

Subjects in the Yin et al.[17] study seemed to benefit the most from probucol administration. The incidence of CIN has been reported to be as high as 19%, however the rate was 13.2% in the Yin et al.[17] study. Patients with AMI may be at higher risk of CIN due to hemodynamic instability and inadequate prophylactic measures.[19] This may be a possible explanation for the greater benefit experienced by patients undergoing primary/urgent PCI.

Wang et al. study is the latest of the studies reviewed and has the lowest risk of bias. It also provides heterogeneity in the present meta-analysis. The authors found that the effect of probucol on CIN was negligible. One possible explanation may be that the incidence of CIN is too low in their study (7.27%, the lowest) to detect any substantial benefit with a limited sample size. Fu et al. observed a similar rate of incidence (7.49%, second lowest), but with a sample size 3 times larger (641 compared to 220). Their study demonstrated a benefit to probucol use. Li et al. also reported a slight but not statistically significant reduction in CIN incidence with a sample size that was similar to that of Wang et al. It is possible that the effect would be significant with a larger sample.

For the adjusted pooled OR, the studies of both Wang et al. and Fu et al. might be at risk of model-overfitting for the multivariate logistic regression analysis. This is particularly true for the Wang et al. study in which there were only 16 CIN events. Additional studies with a larger sample are needed to provide a definite conclusion on whether probucol is independently associated with a reduction in CIN incidence.

Probucol has demonstrated a pleiotropic and lipid-lowering effect, at the expense of the high-density lipoprotein (HDL) level.[20] It has been proposed that despite the reduction, it may enhance the antioxidative function of HDL.[20] Probucol has also been shown to increase long-term survival after complete revascularization.[21] Its potent antioxidative and anti-inflammatory properties may potentially protect the kidney from contrast-induced injury.[10–12] An animal

study indicated that probucol protected against CIN by reducing local renal oxidative stress.[22] Probucol also demonstrated inhibition of renal cell apoptosis by reducing the expression of mitochondrial caspase-3 through regulation of extracellular signal-regulated kinases 1 and 2/c-Jun N-terminal kinase-caspase 3 expressions.[23] Unfortunately, another preclinical study failed to demonstrate a benefit from short-term use of probucol on contrast-induced cytotoxicity of human embryonic kidney cells.[24]

In conclusion, the current meta-analysis showed that probucol did not reduce incidence of CIN, however, due to the low certainty of evidence, further study is required. Although the p-value was not significant, the confidence interval showed a non-significant trend toward benefit, but this trend might be due to publication bias. Probucol appeared to have a promising effect in AMI patients undergoing primary/urgent coronary angioplasty. Further RCTs must be conducted before drawing a final conclusion. As of now, the authors did not recommend the routine use of probucol to reduce CIN in patients undergoing CAG/PCI until there is more solid evidence.

Limitations

Limitations of this systematic review and meta-analysis include the risk of publication bias demonstrated by the asymmetrical funnel plot, and the fact that the studies were not more regionally diverse. The sample size for some studies was inadequate to draw a confident conclusion. We encourage further investigation with a double-blind design and a larger sample. The use of probucol may benefit AMI patients undergoing invasive coronary procedures and it is an interesting area to be explored. Studies of populations outside of Asia are needed to examine probucol use in other groups.

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

Peer-review: Externally peer-reviewed.

Conflict-of-interest: The authors declare that they have no competing interests.

Authorship contributions: R.P. conceived and designed the study and drafted the manuscript. E.Y., and R.V. performed initial search. R.P and A.A.L. performed data extraction, interpreted the data, and performed extensive research on the topic. R.P. performed the statistical analysis. All authors contributed to the writing of the manuscript. All authors have read and approved the manuscript.

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Keywords: Contrast-induced nephropathy; coronary angiography; coronary angioplasty; coronary artery disease; probucol.

Anahtar sözcükler: Kontrast madde nefropatisi; koroner anjiyografi; koroner anjiyoplasti; koroner arter hastalığı; probukol.