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The efficacy of probucol combined with hydration in preventing contrast-induced nephropathy in patients with coronary heart disease undergoing percutaneous coronary intervention: a multicenter, prospective, randomized controlled study

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Abstract
Purpose To investigate the preventive effect of probucol combined with hydration on contrast-induced nephropathy (CIN) in patients with coronary heart disease undergoing percutaneous coronary intervention (PCI).
Methods A total of 641 patients undergoing PCI were randomly assigned to either a probucol group (probucol 500 mg twice daily and hydration; $n = 321$) or a control group (hydration only; $n = 320$). The primary endpoint was the incidence of CIN, defined as an increase in serum creatinine (Scr) by ≥ 44.2 μmol/L or ≥ 25% within 72 h after the administration of contrast agent. Secondary endpoints were changes in Scr, cystatin-C (Cys-C), creatinine clearance rate (Ccr), C-reactive protein (CRP), superoxide dismutase (SOD), and glutathione (GSH) within 72 h, and major adverse events during hospitalization or the 14-day follow-up period.
Results The incidence of CIN was 4.0% (13/321) in the probucol group and 10.9% (35/320) in the control group. The probucol group had lower Cys-C and higher Ccr at 48 and 72 h after PCI compared with the control group. At 48 and 72 h following the operation, Cys-C and CRP were lower in the probucol group compared with the control group, but Ccr, SOD, and GSH were higher. There were no differences in the incidence of major adverse events during hospitalization or the 14-day follow-up between the groups. Multivariate logistic regression analysis showed that probucol was an independent protective factor for CIN.
Conclusions Probucol combined with hydration more effectively decreased the incidence of CIN in patients with coronary heart disease undergoing PCI compared with hydration alone.

Keywords Probucol · Coronary heart disease · Percutaneous coronary intervention · Contrast-induced nephropathy · Prevention

Introduction

Contrast-induced nephropathy (CIN) is a common complication after percutaneous coronary intervention (PCI), defined as an increase in serum creatinine (Scr) by ≥ 44.2 μmol/L or ≥ 25% within 72 h after administration of a contrast agent [1]. CIN has become the third leading cause of hospital-acquired renal injury, responsible for up to 11% of all causes of hospital-acquired renal injury [2]. CIN is associated with prolonged hospitalization as well as increased cardiovascular morbidity, renal morbidity, and all-cause mortality, with some patients requiring dialysis [3]. Strategies have been established to prevent CIN such as identifying high-risk patients who may develop CIN, reducing contrast agent volume, intensifying preprocedural intravenous saline hydration, and using isoosmolar contrast agent (iodixanol) along with bicarbonate hydration [4–6]. However, CIN is still a common serious

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complication after PCI, and effective preventive measures are important.

While the exact pathogenesis of CIN has not been determined, it is generally believed that contrast-mediated renal vasoconstriction, renal ischemia, inflammatory responses, and oxidative stress are the most important components of the pathophysiology of CIN [7, 8].

Probucol is a potent antioxidant and shows significant antioxidative stress and anti-inflammatory ability and improved renal vascular endothelial function [9, 10]. It is widely used in clinical practice for the prevention and treatment of atherosclerosis and diabetic nephropathy because of its strong antioxidative and lipid-lowering effects. Some studies report that probucol plays a prophylactic role in the development of CIN [11, 12], but most of these studies were single-center studies using small sample sizes. The complete nature of the preventive role of probucol in CIN remains unclear.

Given the potential role of oxidative stress in the pathophysiology of CIN and the antioxidant effects attributed to probucol, the current prospective, randomized controlled trial sought to determine whether oral probucol could reduce the incidence of CIN in patients with coronary heart disease undergoing elective PCI.

Methods

Study population

This study was approved by the ethics committees of Tianjin Chest Hospital, Tianjin First Central Hospital, Tianjin Fourth Central Hospital, and Teda International Cardiovascular Hospital. All participants provided written informed consent.

Patients undergoing non-emergent PCI at Tianjin Chest Hospital, Tianjin First Central Hospital, Tianjin Fourth Central Hospital, and Teda International Cardiovascular Hospital between January 2014 and December 2016 were screened for eligibility. Exclusion criteria were: used probucol within 1 week before PCI; allergy to contrast agent; emergency PCI; severe renal insufficiency (defined as creatinine clearance (Ccr) < 30 mL/min; Ccr = [140−age] × weight (kg)/[0.818 × Scr (μmol/L)] (× 0.85 if female); heart failure or left ventricular ejection fraction < 30%; hypotension (systolic blood pressure < 90 mmHg); balloon counter-pulsation treatment; thyroid dysfunction; recent exposure to contrast agent within 2 weeks; electrolyte imbalance; coagulopathy; cardiogenic shock; malignant neoplasms; and acute or chronic infection.

Study protocol

Eligible patients were randomly assigned to either the probucol group or the control group according to a computer-generated random sequence, which was carried out using undisclosed codes and recorded by a nurse. Both the physicians and patients were unaware of the group outcomes and treatment interventions. Because hydration is recognized as the most effective measure to prevent CIN, all enrolled patients were given intravenous sodium chloride at a rate of 1.0 mL^{-1} kg^{-1} h^{-1} from 12 h before to 12 h after the operation (at least 1000 mL hydration preoperatively and postoperatively). Patients in the probucol group received hydration and probucol (Qilu Pharmaceutical Co., Jinan, China) 500 mg twice daily at 1 day before and 3 days after the operation. Patients in the control group only received hydration. Drug delivery and hydration were performed by the nurses. The use of aspirin, clopidogrel, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, beta receptor antagonists, statins, and diuretics was left to the discretion of the cardiologists and according to clinical requirements or recommendations in guidelines. A nonionic, low-osmolar iodinated contrast agent (ioversol; Jiangsu Hengrui Pharmaceutical Co., Nanjing, China) was used in all patients during the procedure. None of the patients received antioxidant intensive statins or N-acetylcysteine therapy. Blood samples were collected at admission and at 48 and 72 h after contrast exposure to measure the levels of blood urea nitrogen (BUN), Scr, cystatin-C (Cys-C), superoxide dismutase (SOD), glutathione (GSH), and C-reactive protein (CRP). Blood test was conducted at a single hospital laboratory, and laboratory staff was blind to the study protocol and patients. The highest Scr level at 48 and 72 h after contrast exposure was used to diagnose CIN.

Study endpoints

The primary endpoint was the incidence of CIN, defined as an increase in Scr by ≥ 44.2 μmol/L or ≥ 25% within 72 h after administration of the contrast agent. Secondary endpoints were changes in Scr, Cys-C, and Ccr within 72 h, and major adverse events (including all-cause mortality, adverse cardiac events, renal replacement therapy, internal bleeding, acute heart failure, emergency PCI or surgical coronary bypass after PCI, and cerebrovascular events) occurring during hospitalization and within the 14-day follow-up period.

Statistical analysis

Normally distributed continuous variables, expressed as mean ± standard deviations (SD), were analyzed using Student's *t* tests. Non-normally distributed continuous

variables, expressed as medians and interquartile ranges, were analyzed using nonparametric tests. Categorical data, expressed as percentages, were analyzed using Chi-squared or Fisher's exact tests. Multivariate logistic regression analysis (method = forward: LR) was used to exclude the influence of confounding factors. A 95% confidence interval (95% CI) was constructed around the point estimate of the odds ratio. Those identified as independent predictors in previous studies were included in the multivariable model [13]. Based on earlier studies [14], it was determined that the incidence of CIN was 13% in the control group. We hypothesized that probucol could reduce the incidence of CIN to 5%. Accordingly, at least 269 patients from each group were required for the power of the test set at 0.95 and statistical level (two-sided) at 0.05. A P value < 0.05 was considered significant (two-sided). All statistical analyses were performed using SPSS software (ver. 20.0; SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics

A total of 708 patients initially met inclusion criteria, with 67 meeting exclusion criteria and being excluded. Finally, 320 patients were randomly assigned to the control group and 321 to the probucol group. A flowchart of the study procedure is shown in Fig. 1. Baseline clinical, biochemical, procedural, and medication characteristics of the 641 patients are listed in Table 1. There were no significant differences in baseline characteristics between the two groups before PCI ($P > 0.05$).

Incidence of CIN and multiple logistic regression analysis

The incidence of CIN was 4.0% (13/321) in the probucol group and 10.9% (35/320) in the control group ($\chi^2 = 10.97$,

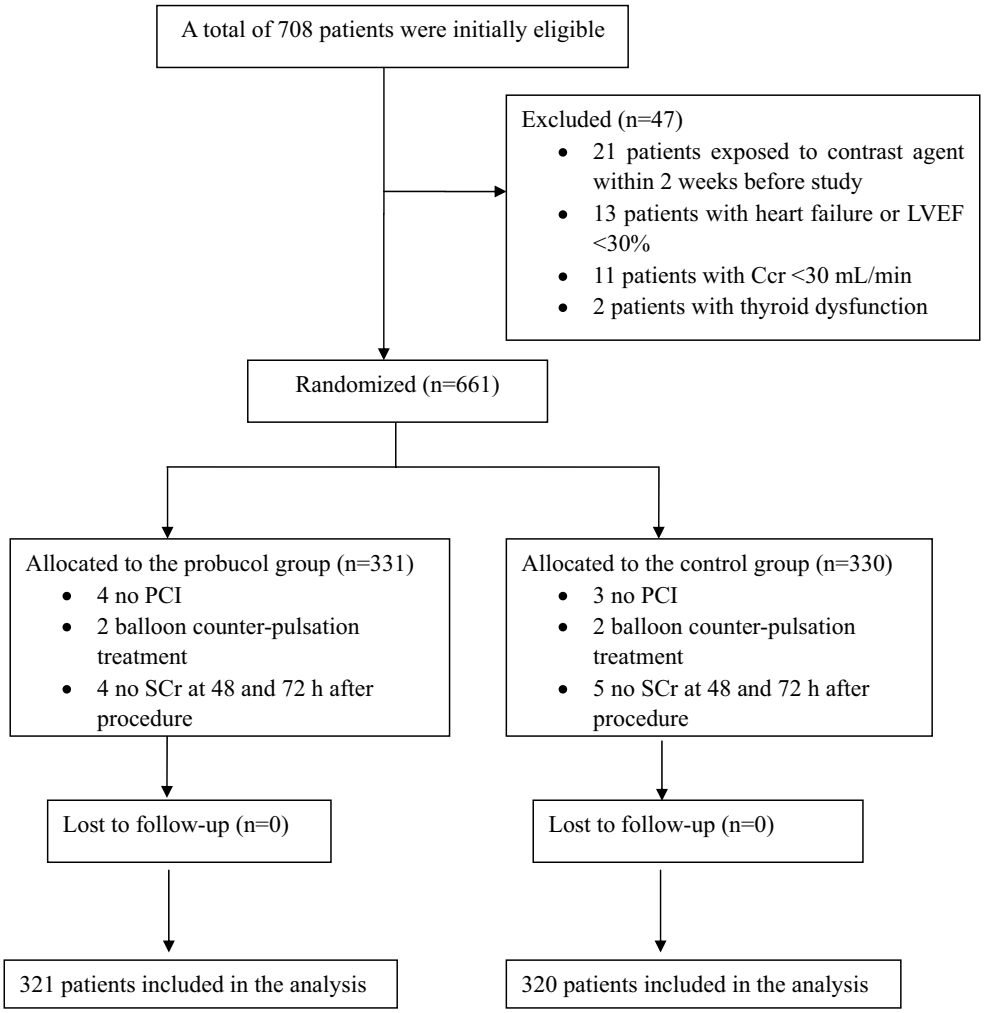

Fig. 1 Flowchart of study protocol

Table 1 Comparisons of baseline characteristics between the two groups

Variables	Probucol group ($n = 321$)	Control group ($n = 320$)	P value
Age (years)	60.33 ± 11.69	61.88 ± 12.35	0.102
Male (%)	184 (57.3)	191(59.1)	0.543
BMI (kg/m^2)	25.05 ± 4.15	24.84 ± 3.92	0.495
Diabetes (%)	83 (25.9)	80 (25.0)	0.803
MI (%)	81 (25.2)	87 (27.2)	0.574
LVEF < 45%	34 (10.6)	36 (11.3)	0.789
Hypertension	193 (60.1)	200 (62.5)	0.537
Ccr < 60 mL/min	69 (21.9)	64 (20.0)	0.641
Contrast volume (mL)	147.45 ± 10.68	149.50 ± 10.56	0.304
Hemoglobin (g/L)	133.91 ± 16.00	133.96 ± 14.49	0.970
Triglycerides (mmol/L)	1.76 ± 0.45	1.75 ± 0.48	0.855
Cholesterol (mmol/L)	4.50 ± 0.76	4.49 ± 0.75	0.801
HDL (mmol/L)	1.05 ± 0.10	1.05 ± 0.11	0.896
LDL (mmol/L)	2.66 ± 0.68	2.68 ± 0.71	0.787
Hydration amount (mL)	1277.18 ± 108.27	1290.24 ± 1128.59	0.427
Aspirin (%)	321 (100)	320 (100)	1.000
Clopidogrel (%)	321 (100)	320 (100)	1.000
β-Antagonist (%)	194 (60.4)	201 (62.8)	0.536
ACEI/ARB (%)	177 (55.1)	169 (52.8)	0.554
Statins (%)	248 (77.3)	243 (75.9)	0.693
Diuretics (%)	39 (12.1)	37 (11.6)	0.903
Calcium antagonists (%)	68 (21.2)	70 (21.9)	0.831

Data are expressed as mean ± SD or *n* (%)

BMI body mass index, *MI* myocardial infarction, *LVEF* left ventricular ejection fraction, *Ccr* creatinine clearance rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers

$P = 0.01$). Multivariate logistic regression analysis was used to analyze possible factors influencing CIN, including myocardial infarction, left ventricular ejection fraction < 45%, contrast volume, diuretics, Ccr < 60 mL/min, diabetes, hydration volume, hypertension, statins, age, and probucol. CIN was used as the dependent variable to exclude confounding factors. Multivariate logistic regression results showed that probucol was a protective factor of CIN (odds ratio 0.342, 95% CI: 0.174–0.672; $P = 0.002$) (Table 2).

Major adverse events during the in-hospital stay and 14-day follow-up period

Major adverse events occurred in seven patients (one death from cardiac rupture, four acute heart failure, one stroke, and one emergency PCI for acute thrombosis) in the probucol group and nine patients (one upper gastrointestinal bleeding, one ventricular fibrillation, six acute heart failure, and one temporary dialysis) in the control group during hospitalization and the 14-day follow-up period (2.2 vs. 2.8%; $\chi^2 = 0.263$, $P = 0.624$). There were no significant differences between the two groups in the incidence of major adverse events.

Table 2 Multiple logistic regression analysis

Variables	OR	95% CI	P value
MI	1.797	0.964–3.349	0.065
LVEF < 45%	0.990	0.944–1.038	0.668
Contrast volume	0.998	0.989–1.008	0.732
Diuretics	0.612	0.274–1.369	0.232
Ccr < 60 mL/min	2.096	0.668–6.579	0.205
Diabetes	1.559	0.805–3.018	0.188
Hydration amount	0.956	0.929–0.984	0.002
Hypertension	0.984	0.523–1.849	0.959
Statins	1.824	0.962–3.457	0.066
Age	1.000	0.998–1.003	0.857
Probucol	0.342	0.174–0.672	0.002

MI myocardial infarction, *LVEF* left ventricular ejection fraction, *Ccr* creatinine clearance rate

Changes in BUN, Scr, Ccr, SOD, GSH, and CRP

Changes in BUN, Scr, Ccr, Cys-C, SOD, GSH, and CRP were compared between the two groups (Table 3). There

Table 3 Changes in BUN, Scr, Ccr, Cys-C, SOD, GSH, and CRP

Variables	Probucol group ($n = 249$)	Control group ($n = 247$)	P value
BUN (mmol/L)			
Baseline	6.75 ± 1.47	6.56 ± 1.62	0.593
48 h post-procedure	6.64 ± 1.45	6.59 ± 1.63	0.485
72 h post-procedure	6.74 ± 1.16	6.68 ± 1.18	0.551
Scr (μmol/L)			
Baseline	87.78 ± 15.42	87.74 ± 11.64	0.752
48 h post-procedure	93.46 ± 19.47*	96.75 ± 22.42*	0.056
72 h post-procedure	91.54 ± 19.79	95.82 ± 13.37	0.077
Ccr (mL/min)			
Baseline	78.23 ± 15.99	78.21 ± 16.41	0.445
48 h post-procedure	72.50 ± 13.46*	69.50 ± 15.57*	0.041
72 h post-procedure	73.29 ± 14.25*	71.51 ± 15.02*	0.035
Cys-C (mg/L)			
Baseline	2.04 ± 0.85	1.99 ± 0.95	0.672
48 h post-procedure	3.08 ± 1.03*	3.69 ± 1.21*	0.039
72 h post-procedure	2.37 ± 1.01*	2.95 ± 1.16*	0.072
CRP (mmol/L)			
Baseline	0.48 ± 0.12	0.48 ± 0.19	0.715
48 h post-procedure	1.98 ± 0.64*	2.14 ± 0.86*	0.003
72 h post-procedure	1.52 ± 0.51*	1.89 ± 0.76*	0.006
SOD (U/mL)			
Baseline	56.29 ± 8.13	56.65 ± 7.61	0.568
48 h post-procedure	71.31 ± 9.16*	69.68 ± 7.94*	0.072
72 h post-procedure	67.31 ± 9.16*	57.68 ± 7.94*	< 0.001
GSH (U/mL)			
Baseline	3.70 ± 0.78	3.68 ± 0.80	0.652
48 h post-procedure	4.93 ± 0.82*	4.86 ± 0.75*	0.094
72 h post-procedure	4.62 ± 0.88*	3.93 ± 0.80*	< 0.001
Incidence of CIN, *n* (%)	13 (4.0)	35 (10.9)	0.001
Incidence of major adverse events, *n* (%)	7 (2.2)	9 (2.8)	0.624

BUN blood urea nitrogen, *Scr* serum creatinine, *Ccr* creatinine clearance rate, *Cys-C* cystatin-C, *IL-6* interleukin-6, *CRP* C-reactive protein, *SOD* superoxide dismutase, *GSH* glutathione

*$P < 0.05$ compared with baseline

were no significant differences in BUN, Scr, Ccr, Cys-C, SOD, GSH, and CRP at baseline between the probucol group and the control group before PCI. In both the probucol group and the control group at 48 and 72 h after the operation, Cys-C, CPR, SOD, and GSH were higher compared with baseline ($P < 0.05$), but Ccr decreased significantly after the operation in both groups ($P < 0.05$). At 48 h after the operation, Cys-C and CRP were lower in the probucol group compared with the control group ($P < 0.05$), but Ccr was higher ($P < 0.05$). At 72 h after the operation, CRP was lower in the probucol group compared with the control group ($P < 0.05$), and Ccr, SOD, and GSH were higher in the probucol group compared with the control group ($P < 0.05$).

Discussion

In this study, we found that administration of probucol 500 mg twice daily 1 day before and 3 days after the operation could reduce the incidence of CIN in patients undergoing a PCI. Probucol combined with hydration appeared is more effective at decreasing the incidence of CIN in patients with coronary heart disease undergoing PCI compared with hydration alone.

The exact pathogenesis of CIN has not been fully determined. It is thought that contrast-mediated inflammatory responses and oxidative stress are the most important factors contributing to the pathogenesis of CIN [7, 8]. Contrast agent filtered by glomeruli, actively taken up by renal tubular cells, and retained within cells and the peritubular

space not only has a direct toxic action on renal tubular cells, increasing oxygen consumption, but also induces vasoconstriction of the vasa recta, decreasing oxygen delivery and inducing hypoxia. Contrast agent triggers a series of reactions that lead to the release of free radicals, causing renal cellular damage and initiating a vicious cycle of oxidative stress and inflammation. A possible treatment strategy for CIN could involve the use of medication that targets the regulators of both renal oxidative stress and inflammation [15, 16].

Probucol is a conventional agent for the reduction in elevated serum cholesterol and has the main chemical composition of 4,4′-[(1-methylethylidene)bis(thio)]bis-[2,6-bis(1,1-dimethylethyl)phenol]. Probucol has antioxidant and anti-inflammatory properties and has been shown to have clinical benefits such as regression of atherosclerosis and reduction in post-angioplasty restenosis in coronary arteries [17, 18]. It is widely used in clinical practice for the prevention and treatment of atherosclerosis [19] and diabetic nephropathy [20] because of its strong antioxidative and lipid-lowering effects. Recent studies have reported that probucol could decrease the incidence of CIN in patients undergoing coronary angiography or PCI. A randomized clinical trial involving 205 patients undergoing coronary angiography or intervention reported that the incidence of CIN was slightly lower in the probucol group compared with the control group (7.84 vs. 14.56%). While not being statistical significant, the post-procedure mean peak of Scr (1.15 ± 0.49 vs. 1.33 ± 0.78 mg/dL; $P = 0.04$) and the post-procedure increase in Scr from baseline (0.15 ± 0.22 vs. 0.25 ± 0.21 mg/dL; $P = 0.001$) in the probucol group were significantly lower than those in the control group [21]. In contrast, Yin et al. [22] found that probucol significantly reduced the incidence of CIN (defined as an increase in Scr ≥ 25% or an absolute increase of ≥ 0.5 mg/dL (≥ 44.2 μmol/L) within 72 h) in high-risk CIN patients with acute coronary syndrome undergoing primary or urgent angioplasty (4.2% (4/96) vs. 21.3% (23/108); $P < 0.001$), and the incidence of Csy-C-based CIN, defined as an increase in serum Csy-C ≥ 10% from baseline within 72 h, was significantly lower in the probucol group (29.2 vs. 51.9%; $P < 0.001$) compared with the control group. In addition, Li Hong et al. [23] found that probucol combined with atorvastatin could reduce serum uric acid levels and improve contrast-induced acute kidney injury in patients undergoing coronary angiography or PCI.

The findings of the current study are consistent with the studies noted above, with the incidence of CIN being lower in the probucol group than in the control group (4.0 vs. 10.9%; $P < 0.05$). At 48 and 72 h after the operation, Cys-C was lower in the probucol group compared with the control group ($P < 0.05$), but Ccr was higher ($P < 0.05$). These results suggest that probucol treatment was associated with a significantly lower incidence of CIN and had a renoprotective effect.

CRP is a sensitive marker of the inflammatory response [24] and is closely associated with CIN [25]. SOD and GSH are indicators of oxidative stress, which can remove oxygen free radicals and prevent lipid peroxidation. In the current study, both the probucol and control groups had higher CRP, SOD, and GSH at 48 and 72 h after the operation compared with baseline ($P < 0.05$), indicating that inflammation and oxidative stress occurred after contrast agent exposure. At 48 and 72 h after the operation, CPR was lower in the probucol group compared with the control group ($P < 0.05$), but SOD and GSH were higher compared with the control group ($P < 0.05$), indicating that treatment with probucol had a certain anti-inflammatory and antioxidative effect. Wang et al. [26] administered probucol to a rat model of CIN and found that it effectively protected renal function, reduced 24-h urinary protein, increased SOD in renal tissue, decreased malondialdehyde content, reduced the proportion of 8-hydroxy-2-deoxyguanosine-positive tubules, and reduced the typical pathological changes associated with CIN, such as tubular epithelial vacuolar degeneration, brush border disintegration and shedding, and mitochondria swelling. Another experimental animal study reported that probucol attenuated the inhibition of renal glutathione peroxidase activity by high iodinated osmolar contrast agent [27]. Recently, a randomized clinical study reported that probucol combined with telmisartan more effectively reduced urinary protein levels than telmisartan alone in patients with diabetic nephropathy by antioxidative stress damage [28]. Taken together, we suggest that the renoprotective effect of probucol may be associated with its antioxidative effect.

This study had some limitations. First, the study excluded patients with severe renal insufficiency (Ccr < 30 mL/min), severe heart failure (left ventricular ejection fraction < 30%), hypotension (systolic blood pressure ≤ 90 mmHg), and emergency PCI. This means that the preventive effects of probucol observed in this study cannot be generalized to patients at high risk of CIN. Second, we only measured CRP, SOD, and GSH; the exact preventive mechanism of probucol on CIN requires further study. Third, the study was not a double-blind study. Therefore, the results need to be validated in larger double-blind multicenter studies.

In conclusion, prophylactic administration of probucol may prevent CIN in coronary heart disease patients undergoing PCI.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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