Int J Clin Exp Med 2018;11(11):12539-12546
www.ijcem.com /ISSN:1940-5901/IJCEM0080017

Original Article

Probucol decreases 8-iso-PGF2α and MMP-9 in patients with unstable angina after percutaneous coronary intervention

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Received May 21, 2018; Accepted August 1, 2018; Epub November 15, 2018; Published November 30, 2018

Abstract: Oxidative stress and lipid peroxidation play important roles in the development of unstable angina (UA). Probucol reduces inflammation and oxidative stress. The aim of this study was to evaluate the effects of probucol on levels of 8-iso-prostaglandin F2alpha (8-iso-PGF2α) and matrix metalloproteinase (MMP)-9 in patients with UA that underwent percutaneous coronary intervention (PCI). This was a single-center prospective cohort study of consecutive adult patients with UA that underwent PCI between March 2016 and July 2016 at the Yidu Central Hospital of Weifang (China). Control patients received conventional medication (aspirin, clopidogrel, rosuvastatin, and isosorbide mononitrate). In addition to conventional therapy, patients in the probucol group took oral probucol (250 mg bid) for 3 months. Levels of 8-iso-PGF2α and MMP-9 were measured the day after PCI and after 3 months. Major adverse cardiac events (MACE) were evaluated during follow-ups (mean of 14 months). Eighty-three patients were enrolled: 40 controls and 43 treated with probucol. Levels of MMP-9 of control and probucol groups were decreased by 14.0% and 47.9%, respectively, at 3 months after PCI (P=0.003). Levels of 8-iso-PGF2α of control and probucol groups were decreased by 13.1% and 49.8%, respectively, at 3 months after PCI (P=0.001). One patient in the control group underwent a coronary angiography for angina pectoris recurrence. There was no acute myocardial infarction or death events in either group during follow-ups. Probucol with rosuvastatin may significantly decrease 8-iso-PGF2α and MMP-9 in patients with UA after PCI.

Keywords: Probucol, rosuvastatin, 8-iso-PGF2α, matrix metalloproteinase 9, percutaneous coronary intervention, unstable angina

Introduction

Unstable angina (UA) is one of the common types of coronary heart disease, with a propensity to progress to acute myocardial infarction or sudden cardiac death [1-4]. Atherosclerosis is a complex process involving oxidative stress, lipid peroxidation, and inflammation [5-8]. Isoprostanes are derivatives of arachidonic acid oxidized by reactive oxygen species (ROS). 8-iso-PGF2α is a stable isoprostane and reliable marker of oxidative stress *in vivo* [9]. In addition, 8-iso-PGF2α has been shown to be a sensitive and independent risk marker of coronary heart disease [10]. Matrix metalloproteinase (MMP)-9 is involved in the degradation of the fibrous cap of atherosclerotic lesions. MMP-9 levels have been directly associated with plaque scores and instability [11]. Monocyte chemoattractant protein (MCP)-1 has been associated with intima-media thickness (IMT), but not with plaque scores or stability. MMP-9 and MCP-1 may be useful biomarkers in distinguishing stable and unstable plaques and predicting future cardiovascular events [12].

Percutaneous coronary intervention (PCI) is recommended for class I patients with UA with severe stenosis [3]. However, PCI itself elicits a systemic inflammatory response that can be measured in the plasma by inflammatory markers C-reactive protein (CRP), interleukin (IL)-6, and serum amyloid A [13, 14]. Release of inflammatory factors after PCI can lead to vulnerable plaque instability and plaque rupture, resulting in adverse cardiovascular events caused by restenosis, stent thrombosis, and endothelial dysfunction [15].

Table 1. Baseline characteristics of the study population (n=83)

Variables	Control group (n=40)	Probucol group (n=43)	P
Age in years (mean ± SD)	64.2±11.8	65.7±9.9	0.518
Male, n (%)	26 (65)	29 (67.4)	0.890
Current smoker, n (%)	19 (47.5)	20 (46.5)	0.493
Diabetes, n (%)	13 (32.5)	16 (37.2)	0.882
Hypertension, n (%)	23 (57.5)	21 (48.8)	0.671
Total cholesterol >5.7 mmol/L, n (%)	6 (15)	7 (16.3)	0.947

Probucol is a synthetic antioxidant, first used as a lipid-lowering drug because it can significantly reduce total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) [16-19]. Probucol has also been used to treat atherosclerosis [20]. Probucol alleviates atherosclerosis by improving HDL function by accelerating the process of reverse cholesterol transport and increasing HDL-associated paraoxonase activity, thereby improving anti-inflammatory and anti-oxidant function [19, 21]. Probucol can decrease plaque areas through decreasing inflammation and oxidative stress [5, 6]. Meng et al. [22] reported that probucol significantly inhibits the generation of ox-LDL and MMP-9. PAS (probucol, aspirin, and atorvastatin) therapy reduces plaque thickness and decreases the rate of adverse events in patients with atherosclerosis [22]. Probucol has also been used in patients that underwent PCI to reduce oxidative stress, incidence of restenosis, and major coronary events after PCI [17, 18, 23, 24].

Data are lacking concerning the effects of probucol on markers of oxidative stress (8-iso-PGF2α) and plaque stability (MMP-9) in patients with UA after PCI. Therefore, the aim of this study was to measure MMP-9 and 8-iso-PGF2α levels in patients with UA that underwent PCI and were treated with probucol and rosuvastatin for 3 months. Patients of the control group were treated with conventional drugs (aspirin, clopidogrel, rosuvastatin, and isosorbide).

Materials and methods

Study design and patients

This was a single-center prospective cohort study of consecutive adult patients with UA that underwent PCI, between March 2016 and July 2016, at the Department of Cardiology of Yidu Central Hospital of Weifang (China). The study was approved by the Human Research Ethics Review Committee. Informed consent was obtained just after the successful procedure, upon successful revascularization without intraoperative death.

Two experienced cardiologists, blinded to clinical and treatment characteristics of the patients, assessed the extent of coronary artery disease and morphology of all coronary artery stenoses. A significant lesion was defined as ≥75% stenosis of the arterial luminal diameter on coronary angiography, according to the ACC/AHA lesion classification scheme (A, B1, B2, or C) [25].

Procedural success was defined as a minimum diameter stenosis of <10% and final thrombolysis in myocardial infarction (TIMI) flow grade 3, without occlusion of a significant side branch, flow-limiting dissection, distal embolization, or angiographic thrombus.

Patient exclusion criteria were: 1) >80 years of age; 2) Pregnant women; 3) Liver or kidney dysfunction; 4) Acute myocardial infarction; 5) Body temperature ≥38.0°C before or during procedure; 6) Inflammatory diseases (infections or autoimmune diseases); 7) Malignancies; 8) Recent major surgery; 9) History of PCI or coronary artery bypass grafting (CABG); or 10) History of statin or antioxidant medication in the previous month.

Treatment

Patients in the control group were treated with oral conventional drugs (lifelong aspirin, 100 mg qd; clopidogrel, 75 mg qd for at least one year; lifelong rosuvastatin, 10 mg qn; and isosorbide mononitrate, 20 mg bid at the time of hospitalization). In addition to conventional therapy, patients in the probucol group took oral probucol (Jingfukang Pharmaceutical Group Co., Ltd., Chengde, China; 250 mg bid) beginning the next day after PCI, for 3 months. Patients were required to avoid other antioxidants during this period.

Blood sampling and enzyme immunoassay

Fasting venous blood samples were collected the next day and 3 months after PCI. Blood samples were centrifuged at 3000 rpm for 15

Table 2. Procedural features in the control and probucol group (n=83)

Variables	Control group (n=40)	Probucol group (n=43)	P
Vessel treated			
Left main	0	1 (1.9%)	0.963
Left anterior descending	24 (47.1%)	24 (46.2%)	0.781
Left circumflex	12 (23.5%)	10 (19.2%)	0.925
Right coronary artery	15 (29.4%)	17 (32.7%)	0.844
Lesion type B2/C	29 (72.5%)	32 (74.4%)	0.924
Multivessel intervention	11 (27.5%)	9 (20.9%)	0.931
Bifurcations with kissing balloon	1 (2.5%)	0	0.963
Number of stents per patients	1.6	1.6	0.796
Stent diameter (mm)	3.1±0.5	3.2±0.6	0.226
Total stent length (mm)	21.9±6.9	20.6±6.1	0.254
Use of drug-eluting stents	40 (100%)	43 (100%)	0.964
Stent deployment pressure	12.9±1.1	13.3±1.1	0.111
Use of post-dilatation	7 (17.5%)	8 (18.6%)	0.943

minutes at 4°C. Plasma was collected and immediately stored at -80°C. MMP-9 and 8-iso-PGF2α levels were measured by enzyme-linked immunosorbent assay (ELISA) kits (TSZ ELISA, Waltham, MA, USA). Effective range was 18-1220 μg/L for MMP-9 and 30-2200 pg/mL for 8-iso-PGF2α, according to Enzyme Analyzer ELISA 400 (Yantai Aidekang Biotechnology Co., China). Routine blood tests were performed, including blood routine, liver function, kidney function, blood glucose, blood lipids, troponin T, and coagulation. Laboratory measurements were performed using standard methods.

Follow-ups

All baseline, clinical, and in-hospital data were obtained, prospectively. Follow-up data were obtained from outpatient clinic visits or telephone calls once a month. Mean follow-up time was 14 months (range, 12-16 months). Follow-ups included asking patients if they had any discomfort, reviewing liver and kidney function, blood lipid analysis, and electrocardiograms, and 24-hour dynamic electrocardiograms, if necessary. Major adverse cardiac events (MACE) were defined as death, non-fatal acute myocardial infarction (MI), and target vessel revascularization (TVR). Regular follow-ups also helped ensure patient compliance.

Outcomes

Primary outcomes were changes in MMP-9 and 8-iso-PGF2α levels after 3 months of treatment. The secondary outcome was occurrence of MACE during follow-ups.

Statistical analysis

Continuous data are presented as mean ± SD (normal distribution) or median (range) (non-normal distribution). Categorical data are presented as counts and proportions (percentages). The normality of distribution of continuous variables was tested using Kolmogorov-Smirnov test. Differences in means were assessed using independent t-test (inter-group analysis) or paired-samples t-test (intra-group analysis). Categorical data were analyzed using Chi-square test. Significance is set at two-sided $P<0.05$ in all tests. Analyses were carried out using SPSS 18 for Windows (IBM, Armonk, NY, USA) by a data analyst blinded to grouping.

Results

Characteristics of patients

Ninety-five patients were screened for eligibility and 83 patients were enrolled: 40 in the control group and 43 in probucol group. Baseline clinical characteristics of enrolled patients are listed in **Table 1**. The age range of the control group was 35-79 years, with males accounted for 65.0%. The age range of the probucol group was 43-78 years, with males accounted for 67.4%. There were no significant differences between the two groups in age, sex, smoking, and main risk factors of coronary heart disease (diabetes, hypertension, and hyperlipidemia) (all $P>0.05$).

Procedural features of the patients are listed in **Table 2**. All patients received at least one drug-eluting stent. There were no significant differences between the two groups (all $P>0.05$).

MMP-9 and 8-iso-PGF2α levels

MMP-9 and 8-iso-PGF2α levels are shown in **Figure 1**. Levels of MMP-9 of control and probucol groups were decreased by 14.0% (from 416±256 to 358±265 μg/L) and 47.9% (from 405±219 to 211±145 μg/L), respectively, at 3

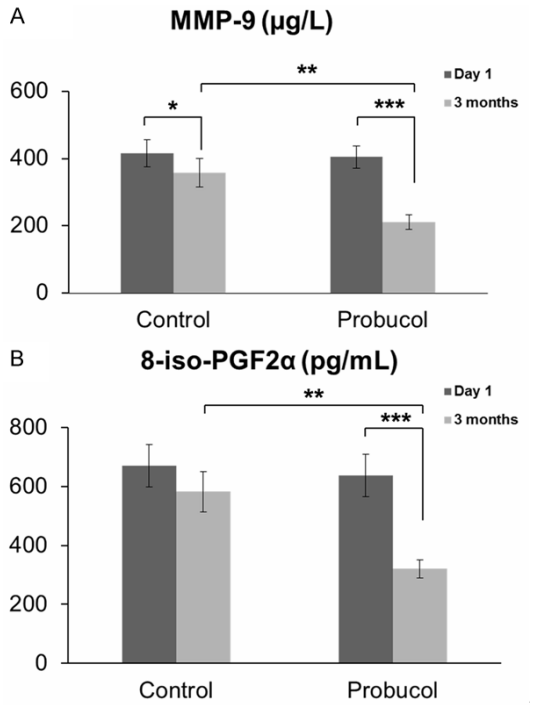

Figure 1. MMP-9 (A) and 8-iso-PGF2α (B) levels of control and probucol groups. *P<0.05; **P<0.01; ***P<0.001 by the t-tests. Error bars indicate 95% CI.

months after PCI (P=0.003). Levels of 8-iso-PGF2α of control and probucol groups were decreased by 13.1% (from 669±454 to 582 ±428 pg/mL) and 49.8% (from 637±477 to 320±200 pg/mL), respectively, at 3 months after PCI (P=0.001). Compared to the control group, both MMP-9 (difference, 95% CI: -147, [-240, -55] μg/L, P=0.002) and 8-iso-PGF2α (difference, 95% CI: -262, [-406, -118] pg/mL, P=0.001) levels in the probucol group were lower at 3 months after PCI.

Blood lipids

Blood lipids are presented in **Table 3**. There were significant decreases in TC (P<0.001) and LDL-C (P≤0.001) 3 months after PCI in the two groups. HDL-C was decreased in the probucol group after 3 months of therapy (P<0.001).

Adverse effects

Three patients in the probucol group felt gastrointestinal discomfort for 3-5 days, but without influencing treatment. No other adverse effects, such as headache, dizziness, paresthesia, tinnitus, insomnia, skin rash, and skin itching, were observed. No electrocardiogram Q-T prolongation, ventricular tachycardia, thrombocytopenia, or abnormal liver or kidney function were found in the two groups.

Major adverse cardiac events during follow-up

No patients were lost to follow-up. One patient in the control group underwent a coronary angiography for angina pectoris recurrence. Additionally, 90% restenosis was determined and another drug-eluting stent was placed four months after the first operation. There were no acute myocardial infarction and death events in either groups during follow-up (P=0.963).

Discussion

Oxidative stress and lipid peroxidation play important roles in the development of UA [5-8]. Probucol reduces inflammation and oxidative stress [16-19]. This study evaluated the effects of probucol on levels of 8-iso-PGF2α and MMP-9 in patients with UA after PCI. Results showed that, compared to the control group, 8-iso-PGF2α and MMP-9 levels of the probucol group were decreased more significantly (47.9% vs. 14.0% and 49.8% vs. 13.1%) after 3 months of treatment. There were significant decreases of TC and LDL-C after 3 months of therapy in the two groups. HDL-C levels were decreased in the probucol group after 3 months. There were no differences in occurrence of MACE in the two groups during follow-up.

The pathogenesis of UA is complex [5-8], generally considered to involve ruptures, erosion, or hemorrhaging of vulnerable plaque, thrombosis, coronary stenosis, spasms, and embolisms, eventually leading to acute or subacute decreases of myocardial oxygen supply. During PCI treatment, a large number of inflammatory cytokines are released from the coronary atherosclerotic plaque due to the direct mechanical effects applied on the atherosclerotic plaque by balloon inflation and stent deployment [13, 14]. The important roles of inflammation in in-stent restenosis are well understood [15]. From animal models and clinical studies, it is known that endothelial injuries, platelet and leukocyte interactions, and subcellular chemoattractant and inflammatory mediators are pivotal in the development of inflammatory responses following stent implantation [26].

Table 3. Blood lipids analysis (before PCI and 3 months after PCI)

Group	Blood lipids	Before PCI Median (range)	3 months after PCI Median (range)	P
Control (n=40)	TG (mmol/L)	1.30 (0.64-3.99)	1.38 (0.65-3.79)	0.090
	TC (mmol/L)	4.11 (2.33-8.32)	3.01 (2.31-4.76)	<0.001
	HDL-C (mmol/L)	1.15 (0.61-1.58)	1.06 (0.57-1.82)	0.440
	LDL-C (mmol/L)	2.03 (1.14-4.27)	1.52 (0.72-3.14)	0.001
Probucol (n=43)	TG (mmol/L)	1.27 (0.40-3.64)	0.85 (0.38-3.15)	0.217
	TC (mmol/L)	4.18 (2.71-6.68)	2.53 (1.63-4.61)	<0.001
	HDL-C (mmol/L)	1.20 (0.85-1.55)	0.97 (0.46-1.42)	<0.001
	LDL-C (mmol/L)	2.16 (1.25-4.02)	1.30 (0.76-3.57)	<0.001

Inflammation is essential for initiation and progression of vascular remodeling, entailing degradation and reorganization of the extra-cellular matrix (ECM) scaffold of the vessel wall, leading to the development of atherosclerotic lesions [5-8]. MMPs are zinc-dependent endopeptidases found in most living organisms, acting mainly by degrading ECM components [27]. MMP-9 is secreted by monocytes, macrophages, endothelial cells, vascular smooth muscle cells, and fibroblasts [27]. MMP-9 is involved in ECM degradation, thereby thinning the plaque fibrous cap [28]. Fiotti et al. [29] showed that MMP-9 expression was significantly higher in patients with acute coronary syndrome, compared with patients with stable angina, after PCI treatment, while high expression of MMP-9 suggests plaque instability and higher risk for adverse cardiovascular events. Therefore, reducing MMP-9 expression could lead to more stable plaque, potentially reducing the risk of major adverse cardiac events after PCI. In the present study, results showed that the decrease of MMP-9 levels was more important after probucol combined with rosuvastatin compared to rosuvastatin alone. These results are supported by a study in cultured cells and apoE knockout mice [6].

Oxidation of lipids, proteins, and nucleic acids is involved in the pathogenesis of many diseases, including atherosclerosis [5-8]. Since circulating 8-iso-PGF2α levels predominantly reflect the production of 8-iso-PGF2α rather than its metabolism and excretion, it can be used as a reliable indicator of oxidative stress *in vivo* [9], supporting its use as a risk marker for CVD [30]. 8-iso-PGF2α levels are significantly higher in patients with UA, compared with matched patients with stable angina and control subjects [31]. Results of the present study showed that the decrease of 8-iso-PGF2α levels was more important after probucol combined with rosuvastatin, compared to rosuvastatin alone.

A previous animal experiment [32] showed that probucol could inhibit macrophage infiltration and expression of MMP-9 in plaque, thereby reducing coronary artery stenosis and increasing plaque stability. Li et al. [33] suggested that probucol may attenuate the enlargement of atherosclerotic vessel walls and may be associated with a negative remodeling pattern, without affecting lumen size. This effect of probucol may involve inhibition of ECM degradation and prevention of apoptosis in atherosclerotic plaques. A randomized controlled trial showed that probucol can significantly decrease ox-LDL-C levels and inhibit expression of MMP-9 in patients with coronary heart disease [22]. A meta-analysis showed that probucol reduced restenosis after PCI [18], supporting the concept of decreased inflammation, oxidative stress, and plaque remodeling.

Reduction of LDL-C levels has been associated with slowed atherosclerosis progression and decreased restenosis after stenting [34]. The present study showed that, in both groups, TC and LDL-C levels were significantly decreased after 3 months of therapy compared with baseline. The decrease of TC and LDL-C in the probucol group was more obvious than in the control group. Results suggested that probucol combined with rosuvastatin could more significantly reduce levels of TC and LDL-C, compared with rosuvastatin alone, probably leading to better long-term outcomes. Longer follow-ups will be necessary to examine this point thoroughly.

Kasai et al. [17] collected data from 1,694 consecutive patients that underwent complete revascularization (PCI and/or bypass surgery). Mortality was compared between patients that received probucol and those that did not. Probucol was associated with significantly reduced risk of all-cause mortality. A meta-

analysis by Liu et al. [18] showed that probucol is more than a lipid-lowering drug, also effective in reducing the risk of restenosis and incidence of MACE after PCI. In the present study, no differences in MACE were observed between the two groups. This could be due to the limitations of the study, including the small sample size and short follow-up. In addition, patients with MI and those with a prior history of PCI or CABG were excluded, reducing the overall risk of MACE in enrolled patients. Furthermore, follow-up angiographies were not performed for some patients, at their discretion. Additional studies are necessary to improve the generalizability of present results.

Probucol with rosuvastatin may significantly decrease 8-iso-PGF2α and MMP-9 in patients with UA after PCI.

Acknowledgements

We would like to thank the participants and staff of the Department of Cardiology. Support was received from the Central Research Laboratories of our institution.

Disclosure of conflict of interest

None.

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References

[1] Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction); American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association of Cardiovascular and Pulmonary Rehabilitation; Society for Academic Emergency Medicine. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American college of cardiology/American heart association task force on practice guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/Non-ST-Elevation myocardial infarction) developed in collaboration with the American college of emergency physicians, the society for cardiovascular angiography and interventions, and the society of thoracic surgeons endorsed by the American association of cardiovascular and pulmonary rehabilitation and the society for academic emergency medicine. J Am Coll Cardiol 2007; 50: e1-e157.

[2] Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, Fesmire FM, Ganiats TG, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK and Zidar JP. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2012; 60: 645-81.

[3] Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members; Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 130: 2354-94.

[4] Braunwald E. Unstable angina and non-ST elevation myocardial infarction. Am J Respir Crit Care Med 2012; 185: 924-32.

[5] Jung YS, Park JH, Kim H, Kim SY, Hwang JY, Hong KW, Bae SS, Choi BT, Lee SW and Shin HK. Probucol inhibits LPS-induced microglia activation and ameliorates brain ischemic injury in normal and hyperlipidemic mice. Acta Pharmacol Sin 2016; 37: 1031-44.

[6] Wang YY, Li H, Wang XH, Yuan M and Li GP. Probucol inhibits MMP-9 expression through regulating miR-497 in HUVECs and apoE knockout mice. Thromb Res 2016; 140: 51-8.

[7] Hajjar DP and Gotto AM Jr. Biological relevance of inflammation and oxidative stress in the pathogenesis of arterial diseases. Am J Pathol 2013; 182: 1474-81.
[8] Uno K and Nicholls SJ. Biomarkers of inflammation and oxidative stress in atherosclerosis. Biomark Med 2010; 4: 361-73.
[9] Roberts LJ and Morrow JD. Measurement of F(2)-isoprostanes as an index of oxidative stress in vivo. Free Radic Biol Med 2000; 28: 505-13.
[10] Schwedhelm E, Bartling A, Lenzen H, Tsikas D, Maas R, Brummer J, Gutzki FM, Berger J, Frolich JC and Boger RH. Urinary 8-iso-prostaglandin F2alpha as a risk marker in patients with coronary heart disease: a matched case-control study. Circulation 2004; 109: 843-8.
[11] Tan C, Liu Y, Li W, Deng F, Liu X, Wang X, Gui Y, Qin L, Hu C and Chen L. Associations of matrix metalloproteinase-9 and monocyte chemoattractant protein-1 concentrations with carotid atherosclerosis, based on measurements of plaque and intima-media thickness. Atherosclerosis 2014; 232: 199-203.
[12] Ma Y, Yabluchanskiy A, Hall ME and Lindsey ML. Using plasma matrix metalloproteinase-9 and monocyte chemoattractant protein-1 to predict future cardiovascular events in subjects with carotid atherosclerosis. Atherosclerosis 2014; 232: 231-3.
[13] Saleh N, Svane B, Jensen J, Hansson LO, Nordin M and Tornvall P. Stent implantation, but not pathogen burden, is associated with plasma C-reactive protein and interleukin-6 levels after percutaneous coronary intervention in patients with stable angina pectoris. Am Heart J 2005; 149: 876-82.
[14] Kozinski M, Krzewina-Kowalska A, Kubica J, Zbikowska-Gotz M, Dymek G, Piasecki R, Sukiennik A, Grzesk G, Bogdan M, Chojnicki M, Dziedziczko A and Sypniewska G. Percutaneous coronary intervention triggers a systemic inflammatory response in patients treated for in-stent restenosis -- comparison with stable and unstable angina. Inflamm Res 2005; 54: 187-93.
[15] Juni RP, Duckers HJ, Vanhoutte PM, Virmani R and Moens AL. Oxidative stress and pathological changes after coronary artery interventions. J Am Coll Cardiol 2013; 61: 1471-81.
[16] Chiesa G, Michelagnoli S, Cassinotti M, Gianfranceschi G, Werba JP, Pazzucconi F, Sirtori CR and Franceschini G. Mechanisms of high-density lipoprotein reduction after probucol treatment: changes in plasma cholesterol esterification/transfer and lipase activities. Metabolism 1993; 42: 229-35.
[17] Kasai T, Miyauchi K, Kubota N, Kajimoto K, Amano A and Daida H. Probucol therapy improves long-term (>10-year) survival after complete revascularization: a propensity analysis. Atherosclerosis 2012; 220: 463-9.
[18] Liu J, Li M, Lu H, Qiao W, Xi D, Luo T, Xiong H and Guo Z. Effects of probucol on restenosis after percutaneous coronary intervention: a systematic review and meta-analysis. PLoS One 2015; 10: e0124021.
[19] Zhong JK, Guo ZG, Li C, Wang ZK, Lai WY and Tu Y. Probucol alleviates atherosclerosis and improves high density lipoprotein function. Lipids Health Dis 2011; 10: 210.
[20] Zhang M, Hou Y, Shen Y, Guo X, Shang D and Zhang D. Probucol reverses homocysteine induced inflammatory monocytes differentiation and oxidative stress. Eur J Pharmacol 2017; 818: 67-73.
[21] Inagaki M, Nakagawa-Toyama Y, Nishida M, Nakatani K, Nakaoka H, Kawase M, Kawase R, Tsubakio-Yamamoto K, Masuda D, Ohama T, Matsuyama A, Ishigami M, Komuro I and Yamashita S. Effect of probucol on antioxidant properties of HDL in patients with heterozygous familial hypercholesterolemia. J Atheroscler Thromb 2012; 19: 643-56.
[22] Meng XP, Wang SX, Zhang JC, Li ZX, Geng L and Yin CY. [Effects of probucol, aspirin and atorvastatin combination therapy upon atherosclerosis]. Zhonghua Yi Xue Za Zhi 2009; 89: 1986-8.
[23] Kaminnyi AI, Lankin VZ, Samko AN, Sozykin AL, Provatorov SI, Konovalova GG, Perepelitsa EI, Tikhaze AK, Polevaya TY, Kukharchuk VV and Belenkov YN. Low daily dose of antioxidant probucol decreases incidence and severity of restenosis after transluminal coronary balloon angioplasty. Bull Exp Biol Med 2005; 139: 183-5.
[24] Kim MH, Cha KS, Han JY, Kim HJ and Kim JS. Effect of antioxidant probucol for preventing stent restenosis. Catheter Cardiovasc Interv 2002; 57: 424-8.
[25] Ellis SG, Vandormael MG, Cowley MJ, DiSciascio G, Deligonul U, Topol EJ and Bulle TM. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. Circulation 1990; 82: 1193-202.
[26] Drachman DE and Simon DI. Inflammation as a mechanism and therapeutic target for in-stent restenosis. Curr Atheroscler Rep 2005; 7: 44-9.
[27] Siasos G, Tousoulis D, Kioufis S, Oikonomou E, Siasou Z, Limperi M, Papavassiliou AG and Stefanadis C. Inflammatory mechanisms in atherosclerosis: the impact of matrix metallo-

proteinases. Curr Top Med Chem 2012; 12: 1132-48.
[28] Fan X, Wang E, Wang X, Cong X and Chen X. MicroRNA-21 is a unique signature associated with coronary plaque instability in humans by regulating matrix metalloproteinase-9 via reversion-inducing cysteine-rich protein with Kazal motifs. Exp Mol Pathol 2014; 96: 242-9.
[29] Fiotti N, Altamura N, Orlando C, Simi L, Reimers B, Pascotto P, Zingone B, Pascotto A, Serio M, Guarnieri G and Giansante C. Metalloproteinases-2, -9 and TIMP-1 expression in stable and unstable coronary plaques undergoing PCI. Int J Cardiol 2008; 127: 350-7.
[30] Davies SS and Roberts LJ 2nd. F2-isoprostanes as an indicator and risk factor for coronary heart disease. Free Radic Biol Med 2011; 50: 559-66.
[31] Cipollone F, Ciabattoni G, Patrignani P, Pasquale M, Di Gregorio D, Bucciarelli T, Davi G, Cuccurullo F and Patrono C. Oxidant stress and aspirin-insensitive thromboxane biosynthesis in severe unstable angina. Circulation 2000; 102: 1007-13.
[32] Li S, Liang J, Niimi M, Bilal Waqar A, Kang D, Koike T, Wang Y, Shiomi M and Fan J. Probucol suppresses macrophage infiltration and MMP expression in atherosclerotic plaques of WHHL rabbits. J Atheroscler Thromb 2014; 21: 648-58.
[33] Li TT, Xie Y, Guo Y, Tian HB, Zhang JN, Peng J and Zhang Y. Effect of probucol on vascular remodeling due to atherosclerosis in rabbits: an intravascular ultrasound study. Chin Med J (Engl) 2011; 124: 1840-7.
[34] Zhang B, Dong X, Zhang Y, Huang R, Yin D, Zheng Z, Liu Y, Zhu H and Zhou X. [Low-density lipoprotein cholesterol target goal attainment rate and related factors in patients with acute coronary syndrome after percutaneous coronary intervention]. Zhonghua Xin Xue Guan Bing Za Zhi 2014; 42: 290-4.