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Original Article

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Effect of Probucol and/or Cilostazol on Carotid Intima Media Thickness in Patients with Coronary Heart Disease: A Randomized, Multicenter, Multinational Study

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Aim: In a prospective randomized multinational open blinded endpoint study, the long-term effects of probucol or probucol and cilostazol with statin on carotid mean intima media thickness (IMT) were evaluated for the first time.

Methods: Hypercholesterolemic patients with coronary artery disease were randomized to three groups and received study drugs for 3 years: the control with statin alone; the probucol group with statin and probucol; and the combo group with statin, probucol, and cilostazol. Primary efficacy endpoint was changes of mean carotid IMT at 3 years. Biomarkers, major adverse cerebro-cardiovascular events (MACCEs) and safety were secondary endpoints.

Results: Two hundred eighty-one patients were randomized into three groups. All three groups showed significant regression of carotid IMT at 3 years compared with baseline. Decrease in mean carotid IMT was significantly greater in the combo group than in the control group at 1 year. However, there were no significant differences in changes of mean carotid IMT between groups at 3 years (control; −0.12 ± 0.36 mm vs. probucol; −0.11 ± 0.32 mm vs. combo; −0.16 ± 0.38 mm). MACCEs were frequent in the control group, but the difference was not significant (control; 10.8% vs. probucol; 4.4% vs. combo; 6.9%, $p = 0.35$). Probucol and cilostazol were well tolerated in long-term treatment without serious drug-related adverse reactions.

Conclusion: Probucol or probucol and cilostazol with statin did not reduce carotid IMT in comparison with statin alone in this study. However, the clinical outcome of probucol-based treatment with current standard statin treatment may need further studies.

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Key words: Coronary artery disease, Probucol, Cilostazol, Carotid intima media thickness

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NCT01291641

Introduction and Aim

β-Hydroxy β-methylglutaryl (HMG) CoA reductase inhibitor (statin) is a cornerstone of treatment for hypercholesterolemia to prevent cardiovascular events. However, there is a need for treatment to reduce residual cardiovascular risk in addition to current standard lipid-lowering treatment with statin. In the "Investigate effect on Mean intima media thickness (IMT) of Probucol And/or CilosTazol in patients with coronary heart dIsease taking HMGCoA reductase inhibitor therapy (IMPACT on IMT)" study, we

evaluated effects of probucol and cilostazol with statin on atherosclerosis progression and biomarkers.

Probucol is effective in lowering cholesterol and has been used to treat hypercholesterolemia[1, 2]. Also, it has antioxidant property[3] and potential to improve surrogates of atherosclerotic diseases[4] and has been effective in preventing progression of carotid atherosclerosis in hypercholesterolemic patients[5]. Although probucol has attractive anti-atherosclerotic properties, it has not been widely used because of its modest cholesterol-lowering effects, high-density lipoprotein (HDL) cholesterol-lowering[6], QT interval prolongation[7], and insufficient clinical evidence supporting its cardiovascular protective effects. Small studies reported that probucol improved long-term outcomes of patients with coronary artery disease[8] and those with familial hypercholesterolemia[9].

Cilostazol is a cyclic adenosine monophosphate phosphodiesterase III inhibitors and used as antiplatelet agents. Previous studies showed that cilostazol had anti-atherosclerotic properties[10, 11], restored endothelial function[12], and modified lipid profiles[13]. Cilostazol was effective to prevent increase in carotid IMT[14, 15]. Cilostazol showed potential to improve cardiovascular outcomes, but results were inconsistent[16, 17].

Several preclinical studies reported additive effects of cilostazol and probucol for atherosclerotic plaque reduction in preclinical studies[18, 19]. Combination of probucol and cilostazol improved endothelial function in patients with silent lacunar cerebral infarct and hypercholesterolemia[20].

In the IMPACT on IMT study, we evaluated effects of probucol or probucol and cilostazol with statin on carotid IMT and biomarkers that reflecting lipid profile, oxidation, and inflammation in patients with coronary artery disease. Carotid IMT was determined as a primary endpoint because it is a well-established surrogate of cardiovascular risk and change in atherosclerosis[21]. To our knowledge, the IMPACT on IMT study is the first long-term prospective study that evaluates effects of probucol and cilostazol with standard statin treatment on carotid IMT in patients with coronary artery disease.

Methods

Population

Five hundred and fifty-eight patients were enrolled between February 2011 and January 2013, and 355 were randomized from five South Korean and 10 Chinese centers. Hypercholesterolemic patients who met the following inclusion criteria were enrolled in the study: 1) age ≥ 20 years, 2) chronic stable coronary disease (≥ 3 months), 3) on treatment with statin, 4) maximal carotid IMT ≥ 1.2 mm, and 5) low-density lipoprotein (LDL) cholesterol ≤ 200 mg/dL. We excluded the patients with homozygous familial hypercholesterolemia, uncontrolled diabetes mellitus, symptomatic heart failure, and prolonged QTc interval. Written informed consent was obtained from each patient, and the trial was approved by the ethics committee of individual participating hospitals.

Study Design (Fig. 1)

The IMPACT on IMT study is a prospective, randomized, multicenter, multinational study. Patients were randomized to one of three groups: 1) a control group that received statin, 2) a probucol group that received probucol (lorelco TM, Otsuka Pharmaceutical Co., Ltd.) 250 mg twice daily and statin, or 3) a combination of probucol and cilostazol (combo) group that received probucol 250 mg twice daily and cilostazol (pletaal TM, Otsuka Pharmaceutical Co., Ltd.) 100 mg twice daily with statin. Statins administered at the time of study entry were continuously administered during the study. Randomization was stratified by country and maximal carotid IMT ≥ 2.0 mm or <2 mm. Planned treatment and observation duration of the study was 3 years.

Primary efficacy endpoint was changes of carotid mean IMT at the end of study (3 year follow up or the last test during study) from baseline. Carotid IMT was measured at baseline and then 1, 2, and 3 years. Secondary efficacy endpoints were the time to major adverse cerebro-cardiovascular event (MACCE; a composite of cardiovascular death, myocardial infarction, cerebral infarction, unstable angina or heart failure requiring hospitalization, or revascularization), occurrence of MACCE, changes of biomarkers, and safety. Biomarkers were measured at baseline, 3 months, and 3 years. Following biomarkers were included: total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and high sensitive C-reactive protein (hsCRP), monocyte chemoattractant protein –1 (MCP-1), and oxidized LDL cholesterol. Safety was evaluated by reported adverse events, physical exam, laboratory test, and electrocardiogram.

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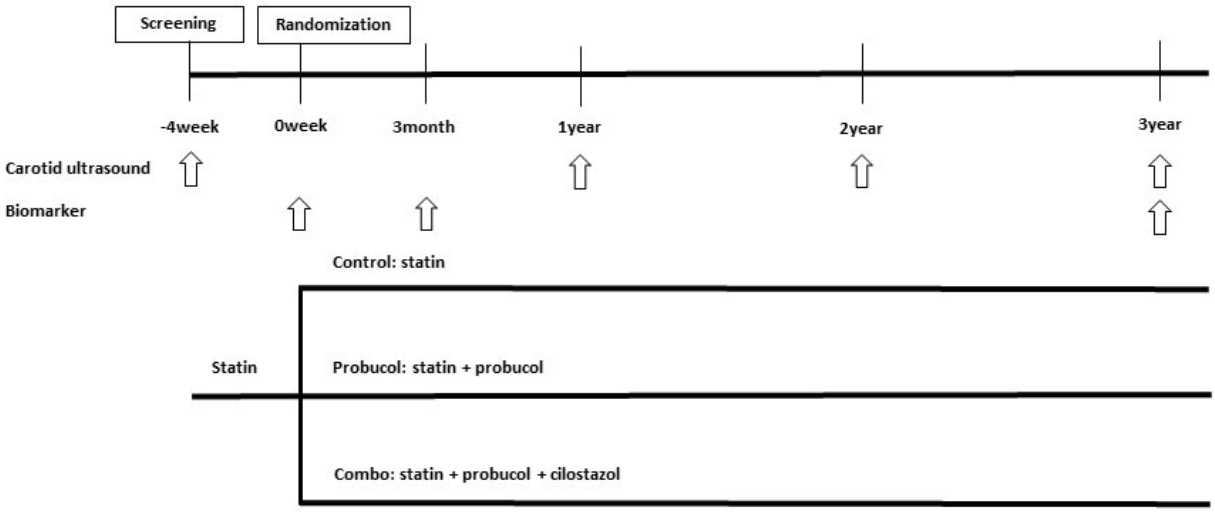

Fig. 1. Study design

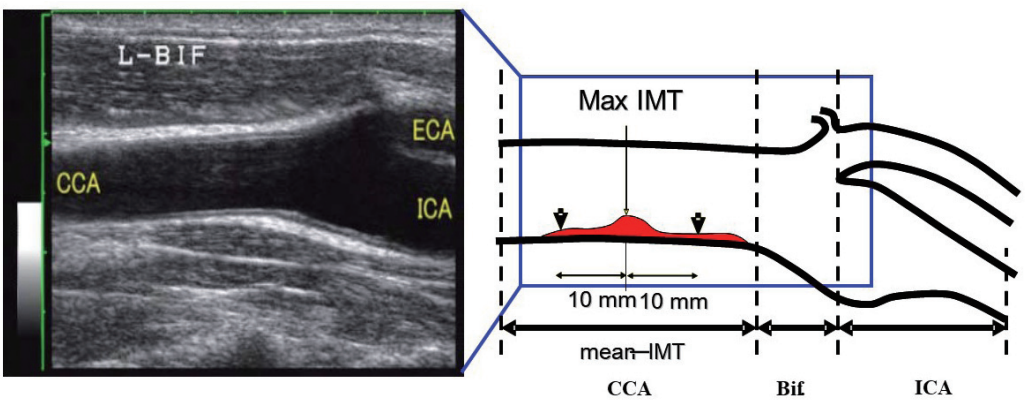

Fig. 2. Measurement of carotid intima media thickness

Mean intima media thickness will be calculated by a mean of two surrounding 100 points on both sides each 10 mm from the point of max intima media thickness. For the same lesion, the same means of measurement and conditions such as ultrasound equipment, patient position, and ultrasound probe angle were applied and the same examiner obtained the carotid ultrasound images during the study.
CCA; common carotid artery, Bif: common carotid artery bifurcation, ECA: external carotid artery, ICA: internal carotid artery

Carotid IMT Measurements (Fig. 2)

Mean carotid IMT was measured by average of values from 100 points within 1 cm from each side of the site giving maximal thickness of carotid IMT. For measurement of carotid IMT, linear probe with 7 MHz or greater was used with scanner condition was adjusted as depth of 30 mm, dynamic range of 65 dB, and 40 frames per second. For the same lesion, the same means of measurement and conditions such as ultrasound equipment, patient position, and ultrasound probe angle were applied, and the same examiner obtained the carotid ultrasound images. Using Intima Scope software (Softmedical, Tokyo, Japan), carotid IMT measurement was done by independent, blinded central laboratory (Matsuo Clinic, Osaka, Japan).

Statistical Analysis

All data were presented as a percentage or mean ± standard deviation. Sample size was based on the estimated mean IMT changes at 3 years. The trial was designed to test superiority of probucol alone or probucol with cilostazol to control. Expected mean additional carotid IMT decrease with probucol compared with control was 0.25 ± 0.6 mm based on FAST study (Sawayama, Shimizu *et al.* 2002). We estimated that a sample size of 342 subjects with assumed dropout rate of 20% would provide approximately 80% power with an alpha level of 0.05. Sample size was increased during enrollment period because of high dropout rate

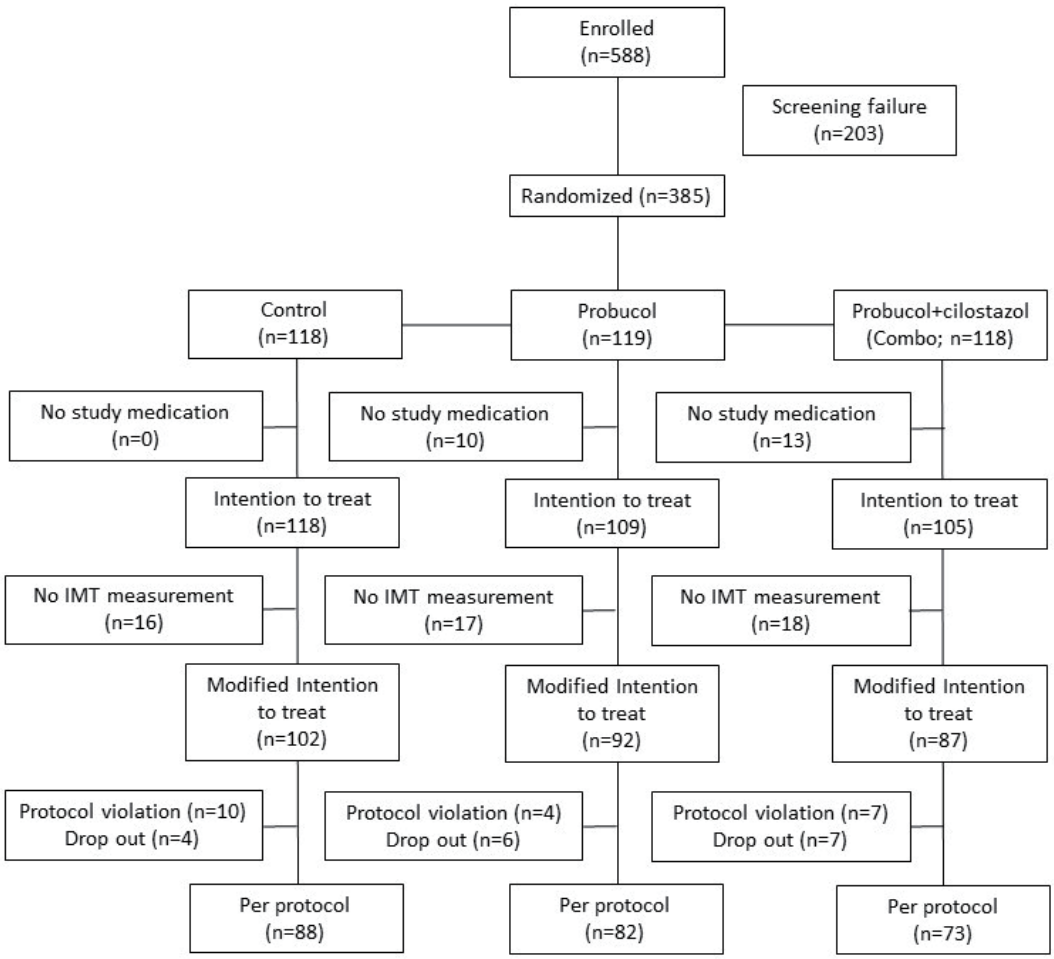

Fig. 3. CONSORT

from 342 to 355 at April 2012. Modified intention to treat (ITT) group was planned to be used for primary efficacy analysis and was defined as subjects who received at least one dose of study drug and had baseline and at least one follow up carotid IMT measurement. Safety analysis was done in ITT group who received at least one dose of study drug. Continuous variables were compared by using *t*-test, Wilcoxon-signed rank test, or Wilcoxon rank sum test. Survival analysis was done via Kaplan–Meier methods. Occurrences of MACCEs were evaluated with chi-square test. Pre-specified subgroup analysis by country and maximal IMT was performed. Independent statisticians performed statistical analysis.

Results

Baseline Characteristics and Study Drug Compliance

Among modified ITT group, 146 (52%) subjects were enrolled from Chinese centers and 135 from Korean Centers **(Fig. 3, Table 1)**. Mean age was 64.1 ± 7.3 years old, and 80% were male. Among them, 41% had diabetes mellitus and 68% had hypertension. Prior to study enrollment, 75% underwent PCI and 32% had history of myocardial infarction. All baseline characteristics were similar between groups except smoking. Proportion of current smokers was significantly lower in the combo group than in the control and probucol groups.

There were no significant differences in use of concomitant drugs except angiotensin-converting enzyme inhibitor or angiotensin receptor blockers **(Table 1)**. Medication compliance during study to probucol was 98.5 ± 8.6% and 97.5 ± 8.5% in the probucol and combo groups, respectively, and compliance to cilostazol was 95.6 ± 8.6%.

Changes of Mean Carotid IMT (Table 2)

After 1 year follow up, mean carotid IMT decreased significantly in all groups, and statistical sig-

Table 1. Baseline characteristics

	Control (n = 102)	Probucol (n = 92)	Combo (n = 87)	p-value
Country				
Korea	48 (47%)	44 (48%)	43 (49%)	0.95
China	54 (53%)	48 (52%)	44 (51%)	
Male	84 (82%)	78(85%)	63 (72%)	0.09
Age, years	63.5 ± 6.8	64.1 ± 7.1	64.9 ± 8.0	0.49
Systolic blood pressure, mmHg	130.9 ± 16.2	128.1 ± 13.4	128.2 ± 13.1	0.49
Diastolic blood pressure, mmHg	76.7 ± 9.8	76.0 ± 8.1	75.5 ± 8.2	0.75
Heart rate, /min	65.8 ± 7.3	66.5 ± 8.2	67.1 ± 8.8	0.70
Smoking	31 (30%)	27 (29%)	12 (14%)	0.01
Previous medical history				
Previous CABG	4 (4%)	3 (3%)	3 (3%)	1.00
Previous PCI	84 (82%)	65 (71%)	64 (74%)	0.13
Previous myocardial infarction	34 (33%)	27 (29%)	28 (32%)	0.83
Diabetes Mellitus	42 (41%)	36 (39%)	38 (44%)	0.42
Hypertension	68 (67%)	63 (68%)	62 (71%)	0.46
Peripheral artery disease	1 (1%)	0 (0%)	1 (1%)	>0.05
Concomitant medication				
Beta blocker	59 (58%)	47 (51%)	43 (49%)	0.46
Alpha and beta blocker	23 (22%)	18 (20%)	20 (23%)	0.83
ACEi/ARB	84 (82%)	70 (76%)	55 (63%)	0.009
Antiplatelets except cilostazol	92 (90%)	86 (93%)	81 (93%)	0.65

CABG: coronary artery bypass graft, PCI; percutaneous coronary intervention, ACEi/ARB: angiotensin coverting enzyme inhibitor/ angiotensin receptor blocker

Table 2. Mean carotid IMT and their changes

	Control (n = 102)	Probucol (N = 92)	Combo (n = 87)	p-value : control vs. probucol	p-value: control vs. combo
Mean carotid IMT, mm					
Baseline	102 1.27 ± 0.42	92 1.26 ± 0.34	86 1.31 ± 0.54	0.70	0.97
1 year	102 1.21 ± 0.39*	92 1.16 ± 0.36*	86 1.16 ± 0.52*	0.32	0.06
2 year	100 1.15 ± 0.37*	86 1.17 ± 0.37*	82 1.20 ± 0.49*	0.68	0.87
3 year	97 1.16 ± 0.40*	84 1.15 ± 0.38*	79 1.14 ± 0.42*	0.93	0.55
3 year (LOCF)	102 1.16 ± 0.39*	92 1.15 ± 0.39*	87 1.15 ± 0.43*	0.99	0.62
Changes of mean IMT, mm					
Baseline to 1 year	-0.06 ± 0.25	-0.10 ± 0.29	-0.15 ± 0.22	0.50	0.0006
Baseline to 2 year	-0.13 ± 0.33	-0.10 ± 0.27	-0.11 ± 0.25	0.34	0.55
Baseline to 3 year	-0.12 ± 0.36	-0.10 ± 0.32	-0.16 ± 0.39	0.58	0.46
Baseline to 3 year (LOCF)	-0.12 ± 0.36	-0.11 ± 0.32	-0.16 ± 0.38	0.77	0.55

IMT: intima-media thickness, LOCF: Last Observation Carried Forward
*indicated within group comparison with baseline $p < 0.05$

nificance of decreases in mean carotid IMT was maintained till end of study (all $p<0.01$). Decrease in mean carotid IMT was significantly greater in the combo group than in the control group at 1 year ($p=0.0006$). Decrease in mean carotid IMT at 3 years from baseline was biggest in combo group; however, the differences between groups were not statistically significant. (control; −0.12±0.36 mm, probucol; −0.11±0.32 mm, combo; −0.16±0.38 mm, control vs. probucol; $p=0.78$, control vs. combo; $p=0.56$).

Covariance analysis adjusted with stratification variables (country, maximal baseline IMT), and smoking did not show statistically significant differences in changes of mean carotid IMT at 3 years from baseline between groups (all $p>0.05$).

Changes of mean carotid IMT were not significantly different among groups at 3 years **(Supplement Table 1)** in per-protocol analysis. In the comparison between control and pooled probucol groups (probucol+combo group), mean carotid IMT decrease was greater in pooled probucol group −0.06±0.26 vs −0.12±0.26 mm, $p=0.017$) at 1 year. However, the difference was not maintained at 2, 3, and end of study **(Supplement Table 2)**.

Subgroup Analysis of Mean Carotid IMT

There were differences in trends of carotid IMT changes by countries **(Supplement Table 3)**. In Korean subgroup, decrease in mean carotid IMT at the end of study was greater in the combo group but difference between groups were statistically insignificant (control; −0.01±0.24 mm, probucol; −0.06±0.23 mm, combo; −0.12±0.33 mm). In Chinese subgroup, all three groups showed significant decreases in mean carotid IMT from baseline at 1, 2, and 3 years. Decreases in mean carotid IMT at the end of study were greater in the control group, but differences between groups were statistically insignificant (control; −0.21±0.41 mm, probucol; −0.15±0.39 mm, combo; −0.19±0.42 mm).

There were no differences in mean carotid IMT changes between groups in both subgroups with maximal carotid IMT <2 mm and ≥ 2.0 mm **(Supplement Table 4)**.

Major Adverse Cerebro-Cardiovascular Events (MACCEs)

Time to MACCEs were not significantly different between groups (control; 986.9±20.8 days, probucol; 1032.7±4.5 days, combo; 973.2±11.9 days, control vs. probucol; $p=0.096$, control vs. combo; $p=0.36$).

MACCEs occurred more frequently in the control group, but the difference was statistically insignificant (control; 10.8% vs. probucol; 4.4% vs. combo; 6.9%, $p=0.35$).

In per-protocol analysis, MACCEs were not different among three groups (control; 8.0% vs. probucol; 3.7% vs. combo; 2.7%, $p=0.25$).

Biomarkers (Table 3)

Mean LDL cholesterol levels of whole study population were 76.4±27.7 mg/dL at baseline, 75.7±32.0 mg/dL at 3 months, and 76.3 mg/dL at 3 years. Total cholesterol, triglyceride, and HDL cholesterol significantly decreased at 3 years compared with baseline in the probucol and combo groups (all $p<0.05$) but not in the control group. Decreases in total cholesterol, LDL cholesterol, and HDL cholesterol at 3 months from baseline were significantly greater in the probucol and combo groups in comparison with the control group respectively (all $p<0.05$), but the statistical significances were not maintained at 3 years except HDL cholesterol.

MCP-1 increased significantly only in the control group at 3 months and 3 years ($p<0.05$). Increases of MCP-1 were greater at 3 years from baseline in the control group than in the probucol group ($p=0.07$) and the combo group ($p=0.04$). Highly sensitive CRP at 3 years significantly increased from baseline in all three groups (all $p<0.05$), but there were no significant differences in changes of hsCRP at 3 years from baseline between groups.

Oxidized LDL cholesterol significantly increased only in the control group ($p=0.008$) and not in the probucol and combo groups at 3 years from baseline. There were no significant differences in changes of oxidized LDL cholesterol at 3 years from baseline between groups.

Safety

Adverse events were observed in 62.7%, 70.6%, and 72.3% in the control, probucol, and combo groups, respectively, and their frequencies were statistically not different ($p=0.25$). Serious adverse reactions were not significantly different between groups (control; 27.9% vs. probucol; 18.4% vs. combo; 26.7%, $p=0.20$). There was one death in the combo group, but the association with the study drug was determined to be unlikely. Drug adverse reactions were more frequently reported in the probucol (36.7%) and combo (53.3%) groups than the control group (4.2%; $p<0.0001$). Frequently reported drug adverse reactions in the probucol or the combo group compared with the control group are QT prolongation, diarrhea, palpitation, headache, and chest pain, and these were previously reported adverse reactions of probucol or cilostazol. The probucol group had

Table 3. Biomarkers

	Control (n=102)	Probucol (n=92)	Combo (n=87)	p-value: control vs. probucol	p-value: control vs. combo
Total cholesterol (mg/dL)					
Baseline	151.3±30.7	151.4±34.7	153.1±31.1	0.83	0.69
3 month	157.2±37.1	127.2±39.6*	132.2±33.2*	<.0001	<.0001
3 year	154.5±39.3	133.8±41.2*	134.2±40.0*	0.0001	0.0001
LDL cholesterol (mg/dL)					
Baseline	75.2±25.7	77.2±30.0	77.2±27.8	0.74	0.78
3 month	82.4±32.1	69.7±33.3*	74.2±29.4	0.0009	0.03
3 year	80.0±36.5	74.6±32.4	73.7±30.0	0.68	0.87
HDL cholesterol (mg/dL)					
Baseline	46.6±12.4	46.4±11.8	49.1±13.9	0.89	0.24
3 month	46.5±11.1	32.8±10.6*	37.2±11.1*	<.0001	<.0001
3 year	47.6±13.3	35.0±14.3*	38.7±14.2*	<.0001	<.0001
Triglyceride (mg/dL)					
Baseline	149.7±86.7	138.7±79.8	135.4±62.6	0.18	0.44
3 month	142.1±66.8	126.4±79.2*	104.3±48.7*	0.01	<.0001
3 year	136.1±66.7	122.7±69.7	110.7±58.9*	0.052	0.004
hsCRP (mg/dL)					
Baseline	0.18±0.45	0.16±0.22	0.13±0.31	0.58	0.23
3 month	0.15±0.37	0.17±0.24	0.15±0.20*	0.06	0.16
3 year	0.28±0.67*	0.18±0.21*	0.17±0.27*	0.26	0.42
MCP-1 (pg/mL)					
Baseline	326.4±186.0	324.2±83.7	339.6±90.5	0.15	0.01
3 month	347.1±174.5*	327.4±103.2	352.8±144.6	0.48	0.48
3 year	358.1±231.1*	326.6±91.5	332.2±79.2	0.53	0.98
Oxidized LDL cholesterol (mg/dL)					
Baseline	263.1±615.0	251.8±543.1	383.3±786.2	0.78	0.30
3 month	302.1±944.7	208.4±357.6	441.6±1029.5	0.83	0.22
3 year	1142.2±6334.5*	276.8±358.8	404.5±755.5	0.78	0.64

*indicated within group comparison with baseline $p<0.05$
LDL; low density lipoprotein, HDL; high density lipoprotein, hsCRP; highly sensitive C reactive protein, MCP: Monocyte chemoattractant protein

only one serious drug adverse reaction, and it was transient liver injury and resolved.

Discussion

Long-term treatment of probucol or combination of probucol and cilostazol with statin was well tolerated in patients with coronary artery disease during 3 years. Probucol was associated with significant lowering of HDL cholesterol as well as total cholesterol, LDL cholesterol, and triglyceride.

In this study, all three groups showed regression of carotid IMT at 1 year, and their changes were maintained until end of study. Decrease in mean carotid IMT was significantly greater in the combo group than in the control group at 1 year. However, in comparison with statin alone at 3 years, either probucol or combination of probucol and cilostazol with statin failed to show further regression of carotid IMT. There was no heterogeneity in changes of carotid IMT in pre-specified subgroup analysis by country, maximal carotid IMT. Intensity of concomitant statin treatment did not influence the response of probucol or probucol and cilostazol to carotid IMT in this study. Majority of patients (93%) enrolled in this study received moderate- or high-intensity statin by classification from 2013 ACC/AHA guideline[22].

Previous studies evaluated effects of probucol, cilostazol, or combination of probucol and cilostazol on regression of carotid IMT[5] or coronary atherosclе-

rosis[23]. In FAST study[5], probucol and pravastatin reduced progression of carotid IMT in comparison with diet only, and baseline LDL cholesterol level was 166.1 mg/dL. Probucol and pravastatin significantly reduced LDL cholesterol in comparison with diet (–24.2%, –32.7%, –5.1% at 12 months, respectively). There was no previous study that evaluated additive effects of probucol on carotid IMT in patients treated with statin. Baseline mean LDL cholesterol of whole population was 76.4 ± 27.7 mg/dL, which were not different between groups. Mean LDL cholesterol difference compared with the control was greatest at 3 months, after then, the differences were attenuated. The difference was statistically significant and –12.7 mg/dL in the probucol group and –8.2 mg/dL in the combo group, respectively. Statistical significance in difference was disappeared at 3 years. This may partly explain the results that the differences in carotid IMT change at 1 year were significantly greater in the combo group, but their differences decreased at end of study. Modest cholesterol-lowering effects of probucol in addition to statin may be insufficient to induce significant further lowering of atherosclerotic burden in relatively short study period. Study duration or sample size might be insufficient to detect differences in carotid IMT with lower baseline cholesterol achieved with statin than previous studies. Also, pleiotropic effects of probucol may not significantly influence the regression of atherosclerotic burden. There were no differences in biomarker level reflecting oxidation and inflammation between groups. In this study, inflammatory biomarkers showed inconsistent results. Highly sensitive CRP was significantly increased at 3 months in the combo group and then in all three groups at 3 years; however, MCP-1 increased in the control group. Oxidized LDL level significantly increased in the control group at 3 years. HDL cholesterol level was significantly lower in both groups receiving probucol than in the control group. Although previous studies suggested that alteration of HDL cholesterol with probucol was not atherogenic[6], effects of the lowering of HDL cholesterol with probucol in patients who were taking statin may need further study.

Additive effect of cilostazol on probucol was not evident in this study. Effects of cilostazol alone to reduce carotid IMT were evaluated in several previous studies with diabetes mellitus[24] and acute coronary syndrome[25], and majority of them reported that cilostazol is effective to slow progression of carotid IMT. However, LDL cholesterol level was not strictly lowered in majority of studies. There are limited numbers of studies that evaluate additive effects of cilostazol with probucol. A small previous study that evaluated effects of the combination of cilostazol and probucol in comparison with cilostazol on coronary atherosclerosis showed negative result[23]. Ongoing PICASSO–IMT study[26] will evaluate effects of combination therapy with probucol and cilostazol on carotid IMT.

Although statistical significance was not reached, patients who received probucol or probucol and cilostazol showed lower incidence of MACCEs in comparison with statin alone during study. This study did not have statistical power to detect effect on clinical outcomes. PROSPECTIVE study to evaluate effects of probucol on secondary prevention in patients with coronary artery is ongoing, and the results will give us more information about role of probucol on cardiovascular outcomes[27]. This study did not support additive effects of cilostazol to probucol in terms of cerebro-cardiovascular events. In previous small study, cardiovascular events were numerically lower in probucol and cilostazol than in cilostazol alone[23]. PICASSO study showed that probucol reduced cardiovascular events in patients with ischemic stroke and suggested potential additive effects of probucol to aspirin or cilostazol[28].

Probucol was associated with QT prolongation. There were no serious arrhythmic events related to probucol in this study although there were concerns related to QT prolongation.

Conclusion

Probucol and cilostazol are well tolerated in long-term treatment without serious drug-related adverse reactions. In comparison with statin alone, probucol or probucol and cilostazol with statin is not effective in reducing carotid IMT. However, further studies may be needed as to the clinical outcome of probucol-based treatment with current standard statin treatment.

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COI

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Supplement Table 1. Mean carotid IMT and their changes in per-protocol analysis

	Control (n = 88)	Probucol (N = 82)	Combo (n = 73)	p-value : control vs. probucol	p-value: control vs. combo
Mean carotid IMT, mm					
Baseline	88 1.28 ± 0.44	82 1.26 ± 0.32	72 1.32 ± 0.55	0.60	0.85
1 year	88 1.22 ± 0.40*	82 1.15 ± 0.34*	72 1.17 ± 0.53*	0.41	0.18
2 year	88 1.14 ± 0.38*	81 1.15 ± 0.33*	73 1.21 ± 0.48*	0.67	0.57
3 year	87 1.16 ± 0.41*	80 1.13 ± 0.32*	72 1.16 ± 0.43*	0.95	0.87
3 year (LOCF)	88 1.16 ± 0.41*	82 1.14 ± 0.33*	73 1.16 ± 0.42*	0.97	0.92
Changes of mean IMT, mm					
Baseline to 1 year	-0.06 ± 0.26	-0.10 ± 0.30	-0.15 ± 0.23	0.53	0.0016
Baseline to 2 year	-0.14 ± 0.35	-0.11 ± 0.27	-0.11 ± 0.26	0.54	0.45
Baseline to 3 year	-0.12 ± 0.38	-0.11 ± 0.32	-0.16 ± 0.40	0.84	0.59
Baseline to 3 year (LOCF)	-0.12 ± 0.38	-0.12 ± 0.33	-0.16 ± 0.40	0.94	0.58

IMT: intima-media thickness, LOCF: Last Observation Carried Forward
*indicated within group comparison with baseline $p < 0.05$

Supplement Table 2. Mean carotid IMT and their changes in control vs. pooled probucol group

	Control (n = 102)	Pooled probucol (N = 179)	p-value : control vs. pooled probucol
Mean carotid IMT, mm			
Baseline	102 1.27 ± 0.42	178 1.28 ± 0.45	0.84
1 year	102 1.21 ± 0.39*	178 1.16 ± 0.44*	0.99
2 year	100 1.15 ± 0.37*	168 1.18 ± 0.43*	0.74
3 year	97 1.16 ± 0.40*	163 1.15 ± 0.40*	0.81
3 year (LOCF)	102 1.16 ± 0.39*	179 1.15 ± 0.41*	0.78
Changes of mean IMT, mm			
Baseline to 1 year	-0.06 ± 0.25	-0.12 ± 0.26	0.017
Baseline to 2 year	-0.13 ± 0.33	-0.11 ± 0.26	0.36
Baseline to 3 year	-0.12 ± 0.36	-0.13 ± 0.35	0.98
Baseline to 3 year (LOCF)	-0.12 ± 0.36	-0.13 ± 0.35	0.86

IMT: intima-media thickness, LOCF: Last Observation Carried Forward
*indicated within group comparison with baseline $p < 0.05$

Supplement Table 3. Mean carotid IMT by country

	Control	Probucol	Combo	*p*-value : control vs. probucol	*p*-value: control vs. combo
Korea					
Baseline	48 1.23 ± 0.33	44 1.23 ± 0.26	43 1.35 ± 0.61	0.63	0.54
1 year	48 1.21 ± 0.31	44 1.17 ± 0.33	43 1.21 ± 0.60*	0.54	0.18
2 year	47 1.18 ± 0.35	40 1.17 ± 0.30*	39 1.25 ± 0.55*	0.88	0.89
3 year	47 1.23 ± 0.39	39 1.18 ± 0.28	39 1.24 ± 0.45	0.81	0.91
3 year (LOCF)	48 1.22 ± 0.39	44 1.17 ± 0.31	43 1.23 ± 0.44	0.69	0.95
China					
Baseline	54 1.31 ± 0.49	48 1.29 ± 0.41	43 1.26 ± 0.47	0.91	0.61
1 year	54 1.22 ± 0.45*	48 1.15 ± 0.39*	43 1.10 ± 0.42*	0.48	0.19
2 year	53 1.12 ± 0.39*	46 1.16 ± 0.42*	43 1.15 ± 0.43*	0.50	0.72
3 year	50 1.10 ± 0.41*	45 1.13 ± 0.44*	40 1.04 ± 0.36*	0.71	0.48
3 year (LOCF)	54 1.10 ± 0.39*	48 1.14 ± 0.45*	44 1.07 ± 0.42*	0.73	0.49

IMT: intima-media thickness, LOCF: Last Observation Carried Forward
*indicated within group comparison with baseline $p < 0.05$

Supplement Table 4. Mean carotid IMT by maximal carotid IMT

	Control	Probucol	Combo	*p*-value: control vs. probucol	*p*-value: control vs. combo
Max IMT < 2.0 mm					
Baseline	74 1.09 ± 0.19	61 1.11 ± 0.21	62 1.12 ± 0.34	0.62	0.95
1 year	74 1.06 ± 0.22	61 1.03 ± 0.26*	62 0.99 ± 0.30*	0.43	0.02
2 year	72 1.00 ± 0.22*	57 1.03 ± 0.25*	59 1.04 ± 0.30*	0.96	0.88
3 year	69 1.01 ± 0.25*	56 1.06 ± 0.29	58 1.02 ± 0.29*	0.25	0.76
3 year (LOCF)	74 1.01±0.24*	61 1.05 ± 0.28	62 1.01 ± 0.29*	0.41	0.47
Max IMT ≥ 2.0 mm					
Baseline	28 1.75 ± 0.49	31 1.56 ± 0.37	24 1.78 ± 0.67	0.08	0.99
1 year	28 1.63 ± 0.43*	31 1.42 ± 0.39	24 1.60 ± 0.68*	0.14	0.48
2 year	28 1.52 ± 0.42*	29 1.44 ± 0.42	23 1.62 ± 0.62*	0.34	0.88
3 year	28 1.54 ± 0.45	28 1.33 ± 0.47*	21 1.46 ± 0.53*	0.03	0.55
3 year (LOCF)	28 1.54 ± 0.45	31 1.35 ± 0.49*	25 1.49 ± 0.54*	0.054	0.34

IMT: intima-media thickness, LOCF: Last Observation Carried Forward
*indicated within group comparison with baseline $p < 0.05$