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Coronary atherosclerotic plaque intervention with Tongxinluo capsule (TXL-CAP): a multicenter, randomized, double-blind and placebo-controlled study

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Clinical evidence of traditional Chinese medicine Tongxinluo capsule therapy on coronary plaque vulnerability is lacking. To investigate whether Tongxinluo may increase coronary plaque stability in patients admitted with acute coronary syndrome based on statin therapy, the TXL-CAP study, a multicenter, randomized, double-blind clinical trial, was conducted. Patients who had a coronary thin-cap lipid-rich plaque detected by optical coherence tomography (OCT) were randomized 1:1 to either Tongxinluo or placebo treatment for 12 months on the basis of guideline-directed treatment. The primary endpoint was the difference in the minimum fibrous cap thickness of the OCT-assessed lesions between Tongxinluo and placebo groups in patients at the end of 12 months. A total of 220 patients were finally recruited and randomized. For the primary endpoint, the minimum fibrous cap thickness did not differ between the two groups at baseline but increased in the Tongxinluo group relative to the placebo group at the 12-month follow-up (115.0 μm vs. 80.0 μm, $P < 0.001$). The increase in the minimum fibrous cap thickness (61.2 μm vs. 33.7 μm, $P = 0.002$) and the decrease in the maximum lipid arc (−38.4° vs. −8.1°, $P = 0.007$) were greater in the Tongxinluo group than in the placebo group. The Tongxinluo group showed improvement in both the Seattle Angina Questionnaire score and the Canadian Cardiovascular Society grading of angina pectoris compared to the placebo group. In conclusion, on the basis of statins, Tongxinluo increased fibrous cap thickness, reduced the lipid arc of coronary thin-cap lipid-rich plaques, and improved angina symptoms without lowering cardiovascular events at the 12-month follow-up in patients with acute coronary syndrome. (http://www.chictr.org.cn, ID: ChiCTR1900025842).

Signal Transduction and Targeted Therapy (2026)11:72 ; https://doi.org/10.1038/s41392-026-02581-z

INTRODUCTION

Since the pioneering work by Erling F, pathological studies have consistently demonstrated that rupture or erosion of culprit atherosclerotic plaques in coronary arteries triggers thrombosis, leading to acute coronary syndrome (ACS), and the concept of "vulnerable plaque" has been adopted to explain the pathogenesis of ACS.[1,2] Recent studies have demonstrated that intervention in vulnerable plaques is effective in preventing adverse cardiovascular events in patients with coronary artery disease (CAD).[3] In addition to culprit lesions, nonculprit lesions may also exhibit a vulnerable plaque phenotype[4] and induce major adverse cardiovascular events (MACE) in patients with ACS. Pathological studies have revealed that a large necrotic core and a thin fibrous cap are the main characteristics of vulnerable plaques.[5] Early studies before the advent of statin therapy showed that a thin-cap fibroatheroma (TCFA) features a necrotic core and a thin fibrous cap of < 65 μm.[6] However, the threshold of 65 μm was derived from the pathological analysis of the ruptured fibrous caps in human specimens.[6] Later, a cutoff value of 80 μm for fibrous cap thickness (FCT) was proposed when analyzing vulnerable plaques in vivo.[7,8] In an early document on the definition of vulnerable plaques, an FCT of <100 μm was defined as a major diagnostic criterion of vulnerable plaque.[9] With the widespread use of statins as the cornerstone therapy for atherosclerosis, the FCT of vulnerable plaques has typically increased by 30–40 μm.[10,11] In recent studies on the efficacy of new lipid-lowering drugs on FCT,

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Received: 22 August 2025 Revised: 3 January 2026 Accepted: 11 January 2026
Published online: 24 February 2026

the baseline values of coronary plaque FCT in recruited patients were all greater than 65 μm.[10,12]

Of current anti-atherosclerotic therapies, statin therapy remains the cornerstone for lowering serum low-density lipoprotein cholesterol (LDL-C) levels and preventing adverse cardiovascular events in high-risk patients. However, residual risk remains in patients with ACS even after high-intensity statin therapy.[13] A recent Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) II study demonstrated that patients with a high lipid content and large plaque burden were at increased risk for future cardiac events.[14] Thus, further development of anti-atherosclerotic therapy in these patients is highly warranted. Tongxinluo (TXL) capsule, a traditional Chinese medicine compound, was authorized to treat angina pectoris and ischemic stroke by the State Food and Drug Administration of China in 1996.[15] The TXL capsule contains 12 ingredients, including *Panax ginseng, Hirudo nipponia, Buthus martensii, Polyphaga plancyi, Scolopendra subspinipes mutilans, Dalbergia odorifera, Santalum album, Boswellia carterii, Ziziphus jujuba, Paeonia lactiflora, Cryptotympana atrata and Borneolum syntheticum*.[15] Studies in our laboratory showed that TXL attenuated and stabilized atherosclerotic plaques in hyperlipidemic animal models via lipid-lowering, antioxidative, anti-inflammatory,[16–18] and intestinal flora-modulating effects.[19] In addition, TXL attenuated lipid accumulation in macrophages by enhancing Beclin-1-induced autophagy.[20] In the CAPITAL study of 1212 patients with carotid atherosclerotic plaques, treatment with TXL capsule for 24 months not only hindered the progression of the mean intima-media thickness (IMT) and the plaque area of the lesions but also reduced the cardiovascular events in these patients.[21] More recently, in the CTS-AMI trial involving 3797 patients with ST-segment elevation myocardial infarction (STEMI), Yang et al. found that treatment with TXL capsules for 12 months improved the short- and long-term clinical outcomes of these patients.[22]

However, the therapeutic mechanism of TXL in patients with atherosclerosis remains obscure. Based on our experimental evidence, a major mechanism underlying the anti-atherosclerotic efficacy of TXL may involve the stabilization of vulnerable plaques. However, whether TXL treatment may stabilize coronary plaques remains elusive. The TXL-CAP trial was designed to test the hypothesis that treatment with TXL capsule may further stabilize coronary plaques by increasing FCT in patients with ACS on the basis of statin therapy.

In the present study, we report the results of the TXL-CAP trial, which evaluated the efficacy of TXL capsule as an add-on therapy to standard statin treatment in patients with ACS. We specifically assessed the impact of TXL on FCT of coronary plaques, a critical structural determinant of plaque vulnerability, using optical coherence tomography (OCT) techniques. This work is important because it not only provides clinical evidence for the potential mechanism of TXL in stabilizing coronary plaques but also offers a promising new therapeutic strategy to improve outcomes in this high-risk patient population.

RESULTS

Baseline characteristics

From October 2019 to May 2021, a total of 1607 patients with ACS were screened from 17 centers in China. Eventually, 220 patients at a mean age of 58.6 years and with male sex of 70.5% who met the inclusion but did not meet the exclusion criteria were enrolled and randomized to TXL ($n = 110$) or placebo groups ($n = 110$) (Fig. 1). The baseline characteristics for the overall population are shown in Table 1 and demonstrated no significant difference between the two groups in age, sex, body mass index, systolic and diastolic blood pressure, history of diabetes, hypertension, smoking, drinking, category lesions by coronary angiography, and administration of major cardiovascular drugs. In particular, statins were administered in 92.7% and 93.6% of patients in the TXL group and the placebo group, respectively. It should be noted that the majority of patients received moderate-intensity statins because such an intensity of statin administration was recommended by the Chinese guidelines for the management of dyslipidemia in adults issued in 2016.[23]

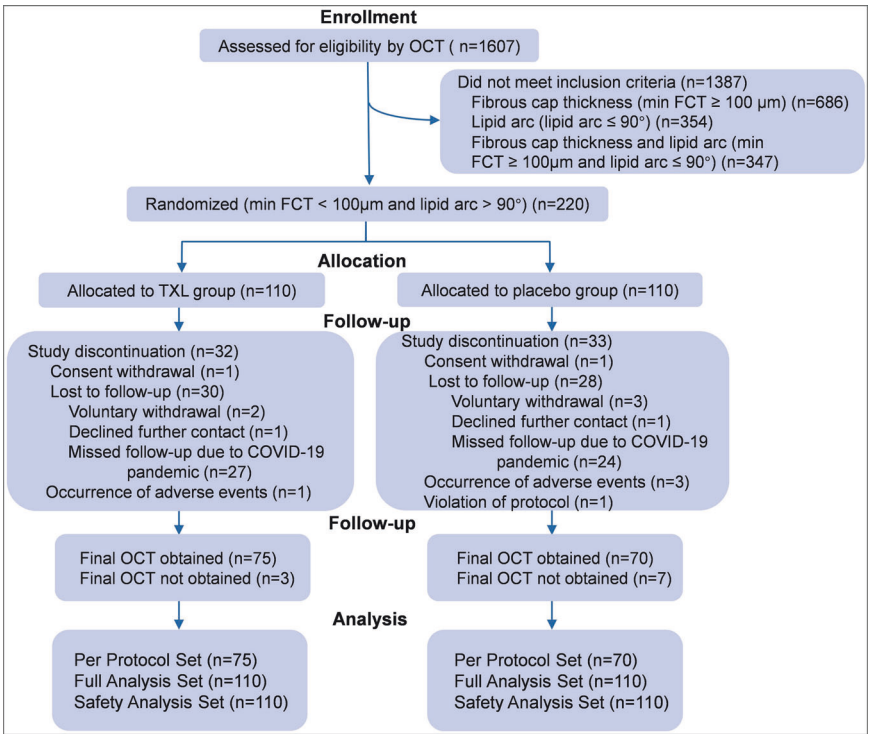


Fig. 1 Flow chart of the TXL-CAP trial. TXL Tongxinluo, OCT optical coherence tomography, min minimum

Table 1. Baseline characteristics of recruited patients in TXL and placebo groups

	TXL group ($n = 110$)	Placebo group ($n = 110$)	*P* Value
Age (year)	58.5 (53.0, 65.0)	59.0 (52.0, 67.0)	0.787
Sex (men, *n*, %)	78 (70.9%)	77 (70.0%)	0.883
Height (cm)	169.0 (162.0,172.0)	170.0 (161.0,172.0)	0.827
Weight (kg)	73.0 (64.0, 80.0)	70.5 (63.0, 80.0)	0.449
BMI (kg/m^2)	25.6 (23.7, 27.8)	25.3 (23.4, 27.7)	0.641
SBP (mmHg)	130.0 (120.0,141.0)	135.5 (121.0, 147.0)	0.125
DBP (mmHg)	80.0 (70.0, 88.0)	80.0 (74.0, 90.0)	0.188
Diabetes (*n*, %)	49 (44.5%)	47 (42.7%)	0.786
Hypertension (*n*, %)	71 (64.5%)	75 (68.2%)	0.568
Smoking (*n*, %)	45 (40.9%)	42 (38.2%)	0.679
Drinking (*n*, %)	26 (23.6%)	30 (27.3%)	0.536
Diagnosis (*n*, %)			
STEMI	31 (28.2%)	22 (20.0%)	0.156
NSTEMI	15 (13.6%)	17 (15.5%)	0.702
UA	64 (58.2%)	71 (64.5%)	0.332
Category lesions[a]			
Category 1 lesions[b]	40 (36.4%)	41 (37.3%)	0.889
Category 2 lesions[c]	54 (49.1%)	54 (49.1%)	1.000
Category 3 lesions[d]	16 (14.5%)	15 (13.6%)	0.846
Baseline medications			
Statin (*n*, %)	102 (92.7%)	103 (93.6%)	0.789
High intensity	2 (1.8%)	3 (2.7%)	1.000
Moderate intensity	100 (90.9%)	100 (90.9%)	1.000
Low intensity	0 (0.0%)	0 (0.0%)	-
Prior Statin use (*n*, %)[e]			0.231
Yes	75 (68.2%)	83 (75.5%)	0.231
No	35 (31.8%)	27 (24.5%)	0.231
Ezetimibe (*n*, %)	17 (15.5%)	16 (14.5%)	0.850
PCSK9 inhibitors (*n*, %)	0 (0.0%)	0 (0.0%)	-
Antiplatelet (*n*, %)	110 (100.0%)	110 (100.0%)	1.000
Beta-blocker (*n*, %)	71 (64.5%)	66 (60.0%)	0.487
ACEI/ARB (*n*, %)	56 (50.9%)	64 (58.2%)	0.279
CCB (*n*, %)	31 (28.2%)	33 (30.0%)	0.767

Values are medians and interquartile ranges (IQR) or *n* (%)
TXL Tongxinluo, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *STEMI* ST-segment elevation myocardial infarction, *NSTEMI* non-ST-segment elevation myocardial infarction, *UA* unstable angina, *PCSK9* proprotein convertase subtilisin/kexin type 9, *ACEI* angiotensin converting enzyme inhibitors, *ARB* angiotensin II receptor antagonist, *CCB* calcium channel blocker
[a]Category Lesions by coronary angiography
[b]diameter stenosis <70% not requiring stent implantation
[c]stenotic lesions with diameter stenosis ≥ 70% that were stented, as well as plaques in other coronary vessels not requiring PCI
[d]stenotic lesions with diameter stenosis ≥ 70% that were stented, and lesions in the same coronary artery located at least 5 mm from the stent edge and not requiring PCI
[e]Prior statin use ≥ 4 weeks before enrollment

Laboratory measurements

Serum levels of total cholesterol (TC) and LDL-C showed a decline from baseline to the end of 12 months in both groups. The extent of serum LDL-C and triglyceride lowering was more significant in the TXL group than in the placebo group. In contrast, the serum levels of high-density lipoprotein cholesterol (HDL-C), blood glucose, cardiac troponin I (cTnI), and high-sensitivity C-reactive protein (hs-CRP) showed no significant changes from baseline to the end of 12 months in either group. These data are presented in Table 2.

Study endpoints

The angiographic data of the culprit lesions at baseline and after percutaneous coronary intervention (PCI) are summarized in supplementary Table 1. No significant differences were observed in the percentage of diameter stenosis, PCI, complete revascularization or residual obstructive CAD between the TXL and placebo groups (all $P > 0.05$). For the OCT-assessed lesions, the values of the minimum FCT did not differ at baseline between the two groups (Table 2). However, after 12 months of treatment, the minimum FCT increased significantly in both groups. By comparison, the minimum FCT as a primary endpoint at the end of 12 months was thicker in the TXL group than in the placebo group (115.0 μm vs. 80.0 μm, $P < 0.001$, Table 2, Fig. 2a).

The statistical analysis in all prespecified subgroups revealed no evidence of significant interaction (Fig. 2b). Specifically, no significant heterogeneity in treatment effect was observed across subgroups stratified by age, sex, type 2 diabetes mellitus, lesion category by coronary angiography, baseline LDL-C, statin intensity, and prior statin use. Imputation modeling for missing at random (MAR) and missing not at random (MNAR) assumptions for patients who did not achieve evaluable OCT imaging during follow-up showed similar findings (supplementary Table 2). All comprehensive sensitivity analyses that adjusted for baseline FCT, center, and time-varying LDL-C, as well as the inverse probability of adherence (IPA) weighting analysis regarding adherence and potential unblinding, also showed similar findings, which robustly supported our primary findings (supplementary Table 3). Furthermore, no significant difference in medication adherence was noted between the two groups (supplementary Table 4).

Representative OCT images in a patient treated with TXL are shown in Fig. 3 who exhibited an increase in minimum FCT from baseline to the end of the 12-month follow-up.

For the secondary efficacy endpoint, the absolute increase of the minimum FCT was higher in the OCT-assessed lesions of the TXL group than those in the placebo group (61.2 μm vs. 33.7 μm, $P = 0.002$, Table 2), and the percentage increase of minimum FCT in the TXL group was also higher than that in the placebo group (83.3% vs. 18.3%, $P < 0.001$). The mean decrease in the maximum lipid arc of the OCT-assessed lesions was greater in the TXL group than in the placebo group (−38.4° vs. −8.1°, $P = 0.007$, Table 2). Additionally, the percentage of decreases in the maximum lipid arc during follow-up was more significant in the TXL group than in the placebo group (-14.8% vs. -8.2%, $P = 0.027$). Moreover, the mean decrease in plaque length from baseline to 12 months was more significant in the TXL group than in the placebo group (−2.5 mm vs. −0.9 mm, $P = 0.037$, Table 2). On the other hand, the percentages of lipid plaque (25.5% in the TXL group vs. 33.6% in the Placebo group, $P = 0.184$), fibrous plaque (15.5% TXL vs. 12.7% Placebo, $P = 0.561$) and calcified plaque (27.3% TXL vs. 17.3% Placebo, $P = 0.075$) were not different between the two groups. The data from the Per Protocol Set (PPS) are shown in the supplementary Table 5.

The imaging features of OCT-assessed lesions were compared between the two groups (supplementary Table 6). The incidence of TCFA was similar at baseline but became significantly lower in the TXL group (1.3%) than in the placebo group (10.0%, $P = 0.029$). After 12 months of follow-up, the proportion of plaques with cholesterol crystals was significantly lower in the TXL group than in the placebo group (10.7% vs. 25.7%, $P = 0.018$). Other imaging features, including macrophage infiltration, calcification

Table 2. Comparison of primary and secondary endpoint outcomes between the Tongxinluo and Placebo groups

	Baseline, median (Q1, Q3)		12-month, median (Q1, Q3)		Change from baseline to 12-month, mean (95% CI)		Difference in change, mean (95% CI)[a]	*P* value[b]
	TXL (*n*=110)	Placebo (*n*=110)	TXL (*n*=110)	Placebo (*n*=110)	TXL (*n*=110)	Placebo (*n*=110)		
Primary Endpoint								
Minimum fibrous cap thickness (μm)	62.5 (60.0, 80.0)	67.5 (60.0, 80.0)	115.0 (70.0,170.0)	80.0 (60.0, 120.0)	61.2 (47.6, 74.7)	33.7 (23.5, 44.0)	27.4 (10.5, 44.3)	0.002
Secondary Endpoints								
Maximum lipid arc (°)	183.6 (145.3, 260.0)	182.7 (143.0, 270.0)	151.2 (115.0, 216.5)	180.2 (120.0, 236.6)	−38.4 (−56.8, −20.0)	−8.1 (−19.8, 3.6)	−30.3 (−51.9, −8.6)	0.007
Plaque length (mm)	10.3 (6.9, 15.0)	9.8 (7.1, 16.2)	8.0 (5.8, 11.1)	9.0 (5.7, 15.3)	−2.5 (−3.7, −1.3)	−0.9 (−1.8, 0.0)	−1.6 (−3.1, −0.1)	0.037
Seattle Angina Questionnaire								
Physical limitation	64.4 (48.9, 80.0)	71.1 (60.0, 80.0)	77.8 (71.1, 80.0)	64.4 (53.3, 76.7)	15.2 (11.4, 19.1)	−2.6 (−6.4, 1.3)	17.8 (12.4, 23.2)	<0.001
Angina stability	50.0 (25.0, 75.0)	50.0 (25.0, 75.0)	100.0 (75.0, 100.0)	75.0 (50.0, 100.0)	46.4 (39.1, 53.8)	28.3 (17.8, 38.8)	18.1 (5.5, 30.8)	0.006
Angina frequency	60.0 (60.0, 80.0)	70.0 (60.0, 80.0)	100.0 (80.0, 100.0)	80.0 (80.0, 95.0)	28.7 (23.9, 33.5)	16.5 (10.9, 22.0)	12.3 (5.0, 19.5)	0.001
Treatment satisfaction	70.6 (58.8, 76.5)	70.6 (58.8, 76.5)	82.4 (76.5, 94.1)	76.5 (64.7, 82.4)	16.3 (12.2, 20.3)	7.3 (3.2, 11.4)	9.0 (3.3, 14.7)	0.002
Disease awareness/QOL	58.3 (33.3, 75.0)	58.3 (41.7, 75.0)	75.0 (75.0, 83.3)	66.7 (58.3, 75.0)	30.7 (24.9, 36.6)	19.1 (14.2, 23.9)	11.7 (4.1, 19.2)	0.003
CCS grade improvement of at least 1 grade, *n* (%)[c]			45 (57.7%)	21 (27.6%)			30.1% (15.2%, 44.9%)	<0.001
Composite cardiovascular events, *n* (%)			5 (4.5%)	11 (10.0%)			−5.5% (−19.0%, 8.2%)	0.119
All-cause mortality, *n* (%)			0 (0.0%)	1 (0.9%)			−0.9% (−14.5%, 12.7%)	1.000
Sudden cardiac death, *n* (%)			0 (0.0%)	0 (0.0%)			-	-
Nonfatal myocardial infarction, *n* (%)			1 (0.9%)	3 (2.7%)			−1.8% (−15.4%, 11.8%)	0.622
Nonfatal stroke, *n* (%)			0 (0.0%)	2 (1.8%)			−1.8% (−15.4%, 11.8%)	0.498
Hospitalization for angina, *n* (%)			2 (1.8%)	4 (3.6%)			−1.8% (−15.4%, 11.8%)	0.683
Hospitalization for heart failure, *n* (%)			0 (0.0%)	0 (0.0%)			-	-
PCI due to ACS, *n* (%)			2 (1.8%)	2 (1.8%)			–0.0% (–13.6%, 13.6%)	1.000
CABG due to ACS, *n* (%)			0 (0.0%)	0 (0.0%)			-	-
Laboratory measurements								
TC (mmol/l)	4.3 (3.5, 5.3)	4.3 (3.6, 4.9)	3.4 (2.9, 4.2)	3.8 (3.0, 4.5)	−1.1 (−1.4, −0.8)	−0.4 (−0.7, −0.1)	−0.7 (−1.2, −0.3)	0.001
LDL-C (mmol/l)	2.6 (1.8, 3.4)	2.6 (1.7, 3.1)	1.9 (1.4, 2.2)	2.1 (1.5, 2.6)	−0.8 (−1.1, −0.6)	−0.4 (−0.6, −0.2)	−0.5 (−0.8, −0.1)	0.004
HDL-C (mmol/l)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)	1.1 (0.9, 1.2)	0.1 (–0.0, 0.2)	–0.0 (–0.1, 0.1)	0.1 (–0.0, 0.2)	0.119
Non-HDL-C (mmol/l)	3.0 (2.4, 4.2)	3.1 (2.5, 3.8)	2.4 (1.6, 2.8)	2.8 (2.0, 3.3)	−1.2 (−1.5, −0.8)	−0.3 (–0.7, –0.0)	−0.8 (−1.3, −0.4)	0.003
Triglyceride (mmol/l)	1.5 (1.1, 2.2)	1.4 (1.0, 2.1)	1.3 (0.9, 1.8)	1.4 (0.9, 2.2)	–0.5 (−0.8, −0.2)	–0.1 (–0.3, 0.1)	–0.4 (–0.8, –0.1)	0.018
ALT (U/l)	21.0 (16.0, 35.0)	23.0 (15.4, 38.0)	20.8 (16.0, 32.0)	25.0 (16.9, 32.0)	−2.7 (–7.4, 2.1)	–0.3 (–5.8, 5.3)	−2.4 (−9.6, 4.8)	0.516
Creatinine (μmol/l)	74.0 (62.0, 84.0)	75.0 (62.0, 87.3)	68.0 (59.0, 82.0)	73.0 (61.6, 84.0)	0.6 (–2.1, 3.3)	0.5 (–3.4, 4.3)	0.1 (−4.5, 4.8)	0.957
Glucose (mmol/l)	6.0 (5.0, 7.7)	5.5 (4.8, 7.5)	5.8 (5.1, 7.0)	5.4 (4.8, 6.2)	–0.4 (−0.9, 0.1)	–0.2 (–1.0, 0.6)	−0.2 (−1.1, 0.8)	0.716

Table 2. continued

	Baseline, median (Q1, Q3)		12-month, median (Q1, Q3)		Change from baseline to 12-month, mean (95% CI)		Difference in change, mean (95% CI)[a]	*P* value[b]
	TXL (*n*=110)	Placebo (*n*=110)	TXL (*n*=110)	Placebo (*n*=110)	TXL (*n*=110)	Placebo (*n*=110)		
cTnI (ng/ml)	0.2 (0.0, 16.6)	0.1 (0.0, 24.0)	0.0 (0.0, 4.8)	0.0 (0.0, 2.6)	−849.4 (−2554.3, 855.6)	−21.9 (−41.4, −2.4)	−827.5 (−2532.5, 877.5)	0.321
hs-CRP (mg/l)	3.0 (1.0, 9.4)	2.0 (0.9, 4.3)	0.5 (0.4, 1.3)	0.9 (0.5, 2.1)	−7.3 (−14.5, −0.1)	3.4 (−6.7, 13.6)	−10.7 (−22.1, 0.8)	0.075

TXL Tongxinluo, *QOL* Quality of Life, *CCS* Canadian Cardiovascular Society, *PCI* Percutaneous Coronary Intervention, *ACS* Acute Coronary Syndrome, *CABG* Coronary Artery Bypass Grafting, *TC* Total Cholesterol, *LDL-C* Low-Density Lipoprotein Cholesterol, *HDL-C* High-Density Lipoprotein Cholesterol, *ALT* Alanine Aminotransferase, *cTnI* Cardiac Troponin I, *hs-CRP* high-sensitivity C-Reactive Protein, *CI* Confidence Interval
[a]Difference in change between groups is marginal differences (95% CI) computed from mixed-effects model adjusting for baseline fibrous cap thickness and center
[b]*P* value for between-group comparison of differences in changes (TXL vs. Placebo)
[c]Analysis of subjects with completed 12-month follow-up: Tongxinluo group, $n = 78$; Placebo group, $n = 76$.

(calcification arc and length) and microchannels, were not significantly different between the two groups.

The number of composite cardiovascular events in the TXL group and placebo group were 5 cases (4.5%) and 11 cases (10.0%), respectively, and two cases in each group underwent revascularization. TXL treatment showed a trend toward reducing composite end events. However, no significant difference was found between the two groups (Table 2).

At the end of 12 months, substantial improvement in angina pectoris was observed in the TXL group relative to the placebo group at the 12-month follow-up. Canadian Cardiovascular Society (CCS) Grade I angina was more commonly found in the TXL group than in the placebo group (92.3% vs. 63.2%, $P < 0.001$, Fig. 2c), and the proportion of patients with CCS grading improved by at least one grade was also significantly greater in the TXL group than in the placebo group (57.7% vs. 27.6%, $P < 0.001$, Table 2). In addition, the quality of life of the patients in the TXL group was significantly improved, as shown by the Seattle Angina Questionnaire (SAQ) scores in Table 2. Importantly, the changes in FCT were negatively correlated with those in CCS grading ($r = -0.28$, $P < 0.001$) and positively correlated with those in physical limitation ($r = 0.438$, $P < 0.001$), angina frequency ($r = 0.206$, $P = 0.013$), and disease awareness ($r = 0.313$, $P < 0.001$). Although changes in CCS angina grades and SAQ scores are largely determined by changes in coronary plaque burden, which was not assessed in this study, symptomatic improvements in our patients were partially induced by coronary plaque stabilization (supplementary Table 7).

Safety analysis

The safety indicators between the TXL and placebo groups were compared, and no significant difference was noted in the overall incidence of adverse events between the two groups. In addition, no significant difference was found in the incidence of drug discontinuation due to adverse events between the TXL and placebo groups (0.9% vs. 1.8%, $P = 1.0$, Table 3). Newly onset digestive symptoms were reported in 5 patients (4.5%) in the TXL group, and there were no cases reported in the placebo group, resulting in a statistically insignificant difference ($P = 0.070$). No cases of renal or liver dysfunction were found in the TXL group (Table 3).

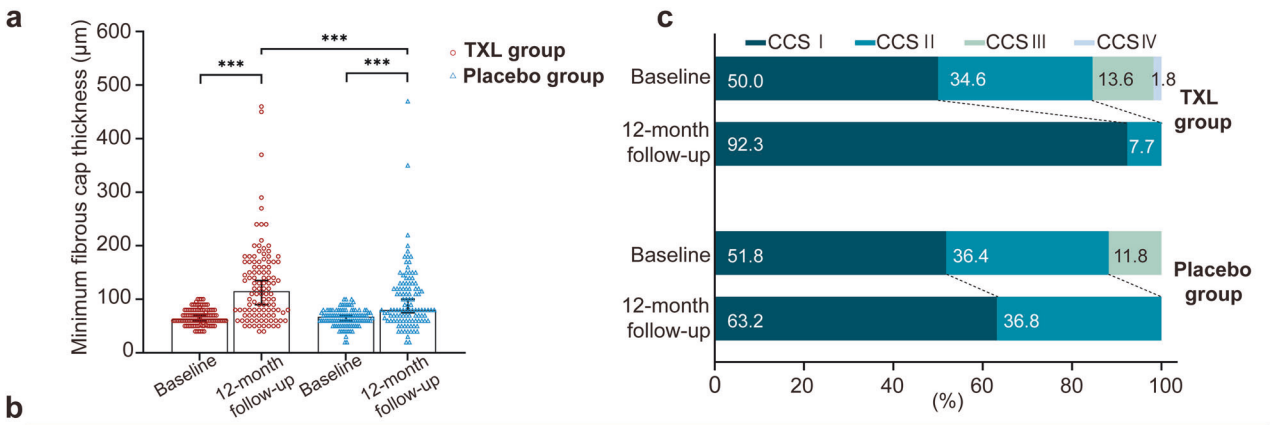
OCT measurement variability

Bland–Altman plots are shown in supplementary Fig. 1. For intraobserver variability analysis, the intraclass correlation coefficient (ICC) for FCT and lipid arc was 0.979 and 1.000, respectively ($P < 0.001$ for both). The interobserver variability analysis indicated that the ICCs for FCT and lipid arc were 0.962 and 1.000, respectively ($P < 0.001$ for both).

DISCUSSION

There were two important findings in the present study. First, on the basis of statin treatment, TXL treatment further increased the minimum FCT and decreased the maximum lipid arc of the OCT-assessed lesions relative to placebo treatment in patients with ACS. Second, TXL treatment attenuated angina severity and improved the SAQ scores and exhibited good safety in these patients. To the best of our knowledge, this is the first clinical study to demonstrate the beneficial effect of the traditional Chinese medicine TXL capsule on the stability of coronary plaques assessed by OCT.

Pathological studies over recent decades have demonstrated that vulnerable plaques are characterized by a large plaque burden, a large lipid-rich core and a thin fibrous cap.[5] Among them, fibrous cap thickness is the main determinant of plaque vulnerability. Early studies before the advent of statin therapy showed that the fibrous cap thickness of thin-cap fibroatheroma



b

Subgroup	n TXL	n Placebo	Change in FCT, Mean (95%CI) TXL	Change in FCT, Mean (95%CI) Placebo	Treatment Difference (95%CI)	P value for Interaction
Age (years)						
< 65	81	76	59.73 (41.58 to 77.89)	34.92 (17.99 to 51.86)	24.81 (3.74 to 45.88)	0.66
⩾65	29	34	46.98 (20.80 to 73.15)	21.06 (-4.39 to 46.51)	25.92 (-8.24 to 60.07)	
Sex						
Women	32	33	76.77 (47.34 to 106.19)	35.35 (8.61 to 62.09)	41.41 (8.65 to 74.18)	0.40
Men	78	77	49.33 (32.69 to 65.97)	28.64 (12.14 to 45.13)	20.70 (0.16 to 41.23)	
Type 2 diabetes mellitus						
Yes	49	47	67.17 (45.52 to 88.82)	24.47 (4.01 to 44.94)	42.70 (17.44 to 67.96)	0.22
No	61	63	53.68 (32.96 to 74.41)	39.10 (19.15 to 59.05)	14.58 (-9.12 to 38.29)	
Lesion category by QCA[a]						
Category 1 Lesions[b]	40	41	63.84 (37.62 to 90.05)	53.86 (28.49 to 79.24)	9.97 (-18.63 to 38.58)	0.15
Category 2 Lesions[c]	54	54	65.09 (43.66 to 86.52)	26.75 (7.51 to 45.99)	38.34 (15.17 to 61.50)	
Category 3 Lesions[d]	16	15	55.57 (8.36 to 102.78)	5.28 (-48.54 to 59.11)	50.29 (-15.50 to 116.07)	
Baseline LDL-C (mmol/l)						
<1.8	27	28	77.05 (38.41 to 115.69)	41.43 (9.17 to 73.68)	35.62 (-1.55 to 72.79)	0.66
⩾1.8	76	76	53.74 (36.67 to 70.82)	35.60 (18.68 to 52.51)	18.15 (-2.58 to 38.87)	
Stain intensity						
Moderate/low-intensity	100	100	61.52 (40.03 to 77.02)	30.65 (15.18 to 46.13)	30.87 (12.67 to 49.07)	0.42
High-intensity	2	3	-3.20 (-594.79 to 588.39)	41.80 (-348.34 to 431.94)	-45.00 (-815.27 to 725.27)	
Prior statin use[e]						
Yes	75	83	59.60 (41.10 to 78.10)	35.07 (18.35 to 51.78)	24.53 (3.40 to 45.67)	0.48
No	35	27	50.78 (28.77 to 72.80)	20.57 (-5.33 to 46.46)	30.22 (-0.04 to 60.48)	

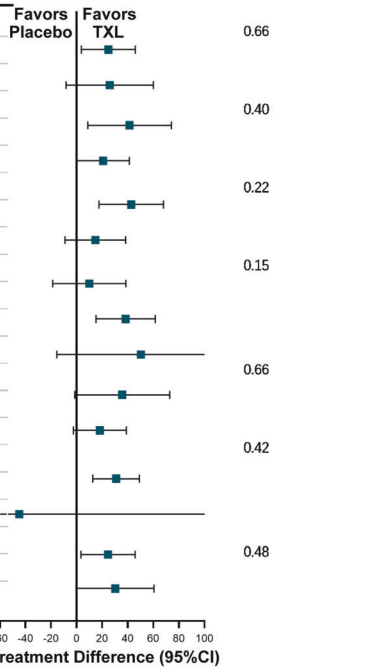


Fig. 2 Primary efficacy and subgroup analysis outcomes at the 12-month follow-up. **a** Comparison of the minimum FCT at baseline and at the 12-month follow-up. Baseline minimum FCT was comparable between the TXL and placebo groups. After 12 months of treatment, FCT increased significantly in both groups, with a greater extent in the TXL group. Data are presented as the median with 95% CI, $n = 110$ per group, ***$P < 0.001$. **b** Subgroup analysis of the treatment effect on the change in FCT. Treatment differences (TXL minus Placebo) in least-squares mean change from baseline in FCT are shown. The *P* values for interaction were provided. No significant difference in treatment effect was observed among patients stratified according to age, sex, type 2 diabetes mellitus, lesion category by coronary angiography, baseline LDL-C, statin intensity, and prior statin use. [a]: QCA: quantitative coronary angiography; [b]: Category 1 lesions: stenotic lesions with diameter stenosis < 70% not requiring stent implantation; [c]: Category 2 lesions: stenotic lesions with diameter stenosis ≥ 70% that were stented, as well as plaques in other coronary vessels not requiring PCI; [d]: Category 3 lesions: stenotic lesions with diameter stenosis ≥ 70% that were stented and lesions in the same coronary artery located at least 5 mm from the stent edge and not requiring PCI; [e]: Prior statin use: prior statin use ≥ 4 weeks before enrollment. **c:** Distribution of angina pectoris severity per the Canadian Cardiovascular Society (CCS) Classification. Bar graphs show the percentage of patients in each CCS (I-V) grading at baseline and at the 12-month follow-up for both the TXL and placebo groups. At the end of the 12-month follow-up, the proportion of patients with CCS Grade I angina was significantly greater in the TXL group (92.3%) than in the placebo group (63.2%, $P < 0.001$). TXL: Tongxinluo; CCS: Canadian Cardiovascular Society; FCT: fibrous cap thickness

(TCFA) was defined as < 65 μm,[6] but this cutoff value of 65 μm was originally derived from pathological studies in human specimens. A minimum FCT of < 120 μm and a lipid arc of > 90° were defined as the inclusion criteria of the HUYGENS study,[12] and the baseline FCT was ~100–110 μm in the PACMAN-AMI trial.[10] In the present study, almost all recruited patients were receiving statin therapy at baseline, which may increase FCT by 30–40 μm,[10,11] and our pilot study showed that the proportion of coronary lesions with a minimum FCT < 65 μm was very low. In addition, a fibrous cap thickness of <100 μm was defined as a major criterion in diagnosing vulnerable plaque by an early expert consensus.[9] Based on previous studies[6,10–12,24,25] and the baseline measurements of FCT in our patients, we defined the minimum FCT < 100 μm and the maximum lipid arc > 90° as the inclusion criteria for our study population.

Despite tremendous achievements in the prevention and therapy of ACS, considerable residual risks of cardiovascular events remain in these patients.[26] Previous studies reported that TXL may exert an effective anti-atherosclerotic effect beyond that of statin therapy. The CAPITAL trial showed that TXL capsule

treatment for 24 months significantly blocked the progression of carotid IMT and plaque area in asymptomatic patients in whom more than one-third of subjects received statin therapy.[21] The

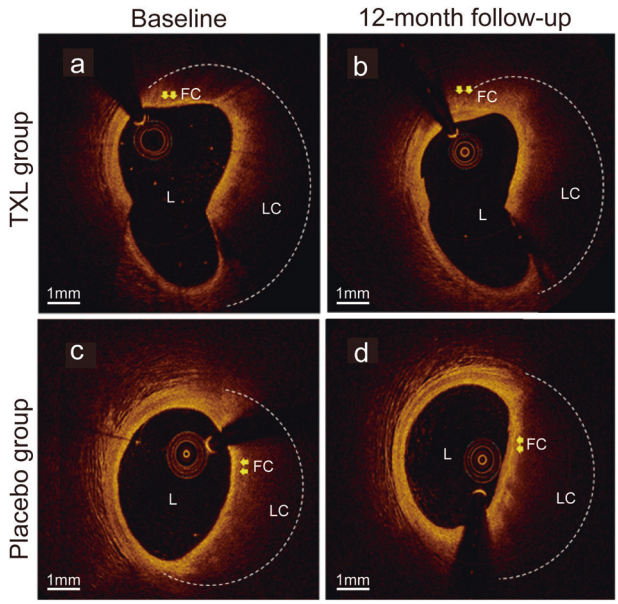


Fig. 3 Representative OCT images showing TXL-induced fibrous cap thickening. a and b: Serial OCT images from a TXL-treated patient. **a** Baseline image of a lipid-rich plaque; **b** The same lesion at 12-month follow-up, demonstrating substantial fibrous cap thickening. **c** and **d**: Serial OCT images from a placebo-treated patient. **c** Baseline image of a lipid-rich plaque; **d** The same lesion at 12-month follow-up, exhibiting minimal change in fibrous cap thickness. The yellow arrowhead indicates the fibrous cap; the dashed line delineates the extent of the lipid core. OCT optical coherence tomography, TXL Tongxinluo, FC fibrous cap, LC lipid core, L vessel lumen. Bar = 1 mm

CTS-AMI trial[22] demonstrated that combined treatment with TXL and statins significantly lowered the 30-day incidence of MACE in patients with acute myocardial infarction, presenting definite clinical benefits. Wu et al. found that TXL administration in combination with guideline-directed medical therapy reduced the frequency of acute episodes and improved the symptoms of angina pectoris.[27] In the current study, TXL capsule administration was effective in alleviating the severity of angina pectoris and improving the SAQ scores in patients with ACS, consistent with previous reports.

To verify whether TXL exerts an anti-atherosclerotic effect by stabilizing vulnerable plaques, we measured the minimum FCT of high-risk coronary plaques and the changes from baseline to 12 months and found that on the basis of statin therapy, TXL treatment significantly increased the FCT of OCT-assessed plaques from 62.5 μm at baseline to 115 μm at the 12-month follow-up. The mean increase in the minimum FCT was 61.2 μm in the TXL group and 33.7 μm in the placebo group after 12 months of treatment, with an intergroup difference in FCT of 35 μm. Previous studies in patients with ACS found a 20 μm to 30 μm difference in the thinnest FCT between ruptured and nonruptured plaques.[7] Notably, the intergroup difference of 35 μm in FCT in the current study exceeded the critical threshold, suggesting that TXL treatment may change high-risk plaques into low-risk ones. Correlative analysis in the present study showed that the increase in FCT correlated with the improvement of angina symptoms, suggesting that the symptomatic relief in our patients was partially induced by coronary plaque stabilization. Additionally, the TXL group showed a significant reduction in maximum lipid arc and plaque length relative to the placebo group, indicating that TXL reduced coronary plaque lipid content and plaque burden. These results were consistent with previous findings demonstrating that the lipid arc and plaque length are independent predictors of plaque vulnerability.[28–30] Our previous studies in a rabbit model of vulnerable plaques[16,17] showed that TXL thickened vulnerable plaque fibrous caps, reduced intraplaque macrophages, and lowered rupture incidence. In the current study, TXL treatment stabilized thin-cap and lipid-rich plaques by

Table 3. Comparison of adverse events between TXL and placebo groups

	TXL group (n = 110)	Placebo group (n = 110)	P value	RR (95%CI)
Patients with any adverse event, *n* (%)	49 (44.5%)	47 (42.7%)	0.892	1.043 (0.772–1.408)
Patients with any serious adverse event (including death), *n* (%)	2 (1.8%)	2 (1.8%)	1.000	1.000 (0.143–6.973)
Adverse events leading to discontinuation of TXL or placebo, *n* (%)	1 (0.9%)	2 (1.8%)	1.000	0.500 (0.046–5.434)
Selected adverse events of interest				
Allergic rash, *n* (%)	2 (1.8%)	1 (0.9%)	1.000	2.000 (0.184–21.737)
Liver dysfunction[a], *n* (%)	0 (0.0%)	2 (1.8%)	1.000	
Renal dysfunction[b], *n* (%)	0 (0.0%)	1 (0.9%)	1.000	
Headache, *n* (%)	3 (2.7%)	0 (0.0%)	0.245	
New-onset symptoms of digestive system, *n* (%)	5 (4.5%)	0 (0.0%)	0.070	
Nausea, *n* (%)	1 (0.9%)	0 (0.0%)	1.000	
Abdominal discomfort, *n* (%)	1 (0.9%)	0 (0.0%)	1.000	
Abdominal distension, *n* (%)	1 (0.9%)	0 (0.0%)	1.000	
Dyspepsia, *n* (%)	1 (0.9%)	0 (0.0%)	1.000	
Chronic gastritis, *n* (%)	1 (0.9%)	0 (0.0%)	1.000	
Bleeding, *n* (%)	1 (0.9%)	3 (2.7%)	0.622	0.333(0.035–3.155)

TXL Tongxinluo, *RR* Relative Risk, *CI* Confidence Interval
[a]Liver dysfunction: abnormal elevation of transaminase during follow-up
[b]Renal dysfunction: defined as serum creatinine increased ≥ 25% or ≥ 0.5 mg/dl at one-year follow-up compared with the basal creatinine by referring to the well-acknowledged diagnostic criteria of acute renal injury

increasing FCT, reducing lipid arc, and shortening plaque length. These animal and clinical studies substantiated the anti-atherosclerotic effects of TXL therapy. Although TXL treatment tended to lower MACE, no significant difference was found compared with the placebo group, which may be related to the limited sample size and short follow-up period in the current study.

The mechanism underlying the beneficial effects of TXL treatment on atherosclerosis is not completely understood. Using high-performance liquid chromatography (HPLC) method, many high content components have been identified from TXL, including ginsenoside Rg1, Rg3, paeoniflorin, acanthopanax saponins, and jujube saponin A. Animal experiments have confirmed a lipid-lowering effect of TXL treatment.[17] In the present study, the serum levels of TC, LDL-C and triglycerides were significantly lower in the TXL group than in the placebo group after 12 months of treatment, although no difference existed in the administration of statin, ezetimibe and PCSK9 inhibitor between the two groups. Considering the intolerance of Chinese patients to high-intensity statins, the Chinese guidelines for the management of dyslipidemia in adults published in 2016[23] and 2023[31] recommended moderate-intensity statins in patients with dyslipidemia. Thus, more than 90% of the recruited patients in this study received moderate-intensity statins, and ezetimibe and PCSK9 inhibitor were not commonly used due to low accessibility to these drugs at the initiation of the study. However, after adjusting for on-treatment LDL-C changes, the beneficial effect of TXL on FCT remained statistically significant. In addition, subgroup analyses revealed no heterogeneity in the effect of TXL on increasing FCT, regardless of statin use and baseline LDL-C levels. These results suggested that the mechanisms underlying the therapeutic efficacy of TXL were independent of lipid-lowering effects and may involve a distinct and direct pharmacological pathway. Although the anti-inflammatory effect of TXL was found in experimental studies,[19,32] hs-CRP, a well-recognized systemic inflammatory biomarker, did not differ significantly between the TXL and placebo groups in the present study, which may be related to the relatively low baseline hs-CRP levels in our enrolled patients. In addition, the anti-inflammatory effect of TXL remains to be verified by more specific inflammatory biomarkers (e.g., IL-6 or TNF-α) in future studies. Another possible mechanism underlying the stabilizing effect of TXL on FCT may involve improved endothelial function by upregulating the expression of endothelial nitric oxide synthase,[33] although this mechanism requires further verification in clinical patients.

An important finding of this study was that no significant difference was found in the overall incidence of adverse events caused by TXL or placebo administration between the two groups of patients. The incidence of drug discontinuation caused by adverse events in the TXL group and placebo group was 0.9% and 1.8%, respectively, which was not significantly different. These results indicated that TXL was safe for long-term treatment.

Our study contains several limitations. First, owing to the impact of the COVID-19 pandemic, some patients were lost to follow-up, and the possibility of selection bias could not be ruled out, which might diminish the impact of our results. However, there was no significant difference in baseline characteristics between patients who completed the study and those lost to follow-up (supplementary Table 8). Furthermore, sensitivity analysis demonstrated that our primary results were robust under different assumptions about the missing data. Although we cannot completely rule out selection bias, these analyses increased our confidence in the internal validity of the trial's conclusions. Second, although there was a trend toward reduced composite cardiovascular events in the TXL group compared with the placebo group, our study was underpowered to detect such a difference in secondary endpoints. Further large sample and long follow-up studies are needed to assess the therapeutic effect of TXL on cardiovascular events. Third, only Chinese patients were enrolled in this study, which may limit the immediate generalizability of our findings to other ethnic groups. Future studies in diverse populations are warranted to confirm the beneficial effect of TXL on plaque stabilization globally.

In conclusion, on the basis of statin therapy, TXL treatment increased the minimum fibrous cap thickness and decreased the maximum lipid arc of coronary thin-cap lipid-rich plaques in patients with ACS. Furthermore, TXL treatment attenuated the severity of angina pectoris and improved the SAQ scores with a good safety profile. Our results provide evidence that on top of statin therapy, treatment with TXL further stabilized coronary atherosclerotic plaques in patients with ACS, which may explain the beneficial effects of TXL on cardiovascular events observed in clinical trials. Larger-scale, longer-term randomized controlled trials with hard clinical endpoints are warranted to further validate the effects of TXL on plaque progression and stability and explore its underlying mechanisms.

Materials and methods (see supplementary materials I for details)

Design and eligibility. The TXL-CAP study was an investigator-initiated, multicenter, randomized and double-blind clinical trial that was conducted in 17 medical centers in China. The protocol of the trial has been published previously.[34]

The trial was approved by the Ethics Committee on Scientific Research of Qilu Hospital of Shandong University [No. 2021(069)] (Supplementary Materials II). The study was performed in accordance with the principles of the Declaration of Helsinki and registered at http://www.chictr.org.cn with the number ChiCTR1900025842.

Subjects underwent a comprehensive baseline screening for eligibility. The inclusion criteria were[34]: (1) patients who were 18 to 80 years old; (2) patients meeting the diagnostic criteria of ACS by 2015 European Society of Cardiology (ESC) Guidelines[35]; and (3) the OCT-assessed lesion had a fibrous cap thickness < 100 μm and lipid arc > 90° as determined by OCT technique that was not treated by PCI. If there were multiple lesions that met this criterion, the plaque with the thinnest fibrous cap was chosen as the OCT-assessed lesion, which could be one of the following[34]: (1) stenotic lesions with a diameter stenosis < 70% without the need for stent implantation; (2) stenotic lesions with diameter stenosis ≥ 70% were stented, and plaques in other coronary vessels that did not require PCI were selected as OCT-assessed lesions; (3) stenotic lesions with diameter stenosis ≥ 70% were stented, and lesions in the same coronary artery that were located at least 5 mm away from the edge of the stent and did not require PCI were selected as OCT-assessed lesions. Thus, the OCT-assessed lesions were divided into three categories according to the aforementioned definitions.

Exclusion criteria included left main coronary disease and/or right coronary artery orifice stenosis; medical history of type 1 diabetes; familial hypercholesterolemia; requiring warfarin for anticoagulation; Takayasu arteritis; severe liver and/or kidney dysfunction; severe chronic obstructive pulmonary disease or respiratory failure; and gastrointestinal, respiratory or other organ bleeding within the previous month.[34] All patients or their legal authorized representatives signed written informed consent before randomization.

Randomization and blinding

Patients were randomized to the TXL group or the placebo group at a 1:1 ratio. The information of an eligible patient was entered into a central randomization system, which generated a double-blind random number for enrolled patients. Patients who met the criteria first completed the baseline assessment. The investigators then logged into a randomization and trial supply management (RTSM) system to generate random patient numbers and the corresponding drug numbers in the order of enrolling time. All

participants in the trial were blinded to the allocation of treatment. The details are presented in the study protocol in Supplementary Materials I.

Procedures

Drug administration and follow-up. After randomization, patients in the TXL group were treated with an oral dose of TXL capsule (4 capsules, 1.04 g) three times daily for 12 months. The placebo group received a placebo capsule that was completely the same as a TXL capsule. The details of the study drugs, including TXL capsule and placebo, are described in Supplementary Materials III. During the entire study period, other proprietary Chinese medicines that contain the same ingredients as TXL capsules were prohibited. All patients received treatment recommended by the ESC guidelines for ACS, including dual antiplatelet agents and statins. The intensity of statin administration adhered to the 2016 Chinese Guidelines for the Management of Dyslipidemia, which recommended a moderate intensity of statin therapy.[23] Patients were followed up for 12 months.

OCT image acquisition and analysis

Patients underwent OCT examination after coronary angiography at the beginning and the end of 12 months of the trial. An OCT system was used, and images were acquired as previously reported.[36] All coronary plaques imaged by OCT were divided into three types: lipid plaques, fibrous plaques, and calcified plaques. Lipid plaques manifested as poor signal regions with diffuse borders and exhibited both enhanced backscattering and attenuation. To ensure an accurate measurement, the entire plaque was first scanned by an OCT catheter along its longaxis and imaged at 1-mm intervals along the longaxis to determine the cross-sectional image with the thinnest FCT and the largest lipid arc, which were used for measurement of FCT and lipid arc. The lipid plaque length was measured in the longitudinal imaging view. All measurements were repeated 3 times, and the values were averaged. Fibrous plaques manifested as homogeneous hyperintense regions, and calcified plaques manifested as well-demarcated hypointense regions interspersed with hyperintense foci.[37,38] In addition, plaque calcification arc and length, macrophage infiltration, cholesterol crystal and microchannels depicted by OCT were recorded. Macrophage infiltration was defined as hyperintense punctate areas—either discrete or confluent—that exhibited higher signal intensity than the background speckle noise. Cholesterol crystals were defined as linear, highly back-scattering structures within the plaque. Microchannels were identified as small lacunar structures within plaques, with a diameter ranging from 50 μm to 300 μm, and were required to be visible on no fewer than three consecutive imaging frames. A lipid plaque occupying ≥ 2 quadrants with an FCT < 65 μm was defined as TCFA.[39]

To verify the reproducibility of OCT measurements, two key variables, FCT and lipid arc, were measured twice in 60 randomly selected patients by two independent experts. Interobserver variability was evaluated between the two experts, and intraobserver variability was evaluated by one expert at different times. Bland–Altman plots were used to analyze the interobserver and intraobserver variability, and ICCs were calculated.

Laboratory assessment

Fasting blood samples were obtained from all recruited patients. The serum levels of lipids, blood glucose, cTnI and hs-CRP, as well as liver and renal functions, were measured at baseline and during follow-up.

Study outcomes

The primary endpoint was the difference in the minimum FCT of the OCT-assessed coronary lesions between the TXL and placebo groups at the end of the 12-month follow-up. Secondary endpoints included the changes in the minimum FCT of the OCT-assessed lesion in the TXL and placebo groups from baseline to 12 months; the changes in maximum lipid arc and length of the OCT-assessed plaque from baseline to 12 months; the percentage of lipid, fibrous and calcified plaques at the end of 12 months of follow-up; the incidence of composite cardiovascular events at 12 months; severity of angina pectoris according to the criteria of the Canadian Cardiovascular Society[40]; SAQ score[41]; and serum hs-CRP levels.[34]

The baseline severity of angina pectoris in enrolled patients was assessed before discharge. Clinical events were recorded by the researchers and submitted to the Clinical Endpoint Committee (CEC), which was independently reviewed and determined by two members of the Committee, and disputed endpoint events were reassessed by all members of the Committee.

Adverse events related to drug treatment were adjudicated and evaluated by CEC blinded to treatment allocation, regardless of whether they were causally related to the study drug.

Data analysis

The sample size of the TXL-CAP trial was estimated based on a previous report.[42] In the current study, the standard deviation (SD) was assumed to be 0.07 mm for both groups of patients. To detect a mean difference of 0.03 mm between the TXL group and the placebo group with 80% statistical power, a sample size of 87 subjects per group is required when a two-sided Type I error rate (α) is set at 0.05. Assuming a 20% dropout rate, a total of 220 subjects (110 in TXL and 110 in placebo) are needed to obtain final sample sizes of 87 in each group. The sample size calculation software used was PASS 13. Details of the statistical analysis plan (SAP) are available in Supplementary Materials IV.

Continuous variables were expressed as the mean ± SD. Nonnormally distributed data were summarized as medians (Q1-Q3). Categorical variables are described as numbers (%). Normally distributed continuous variables were analyzed using the two-sample t test, and nonnormally distributed continuous variables were assessed via the Wilcoxon rank-sum test. Categorical data were compared using the chi-square test or Fisher's exact test.

Efficacy analysis was performed on the full analysis set (FAS). Supportive analysis was also conducted to supplement the primary findings based on the PPS population. Safety analysis, including adverse events, toxicity and laboratory measurements, was performed in the Safety Analysis Set.

We conducted an initial analysis of the primary outcome using the Wilcoxon rank sum test due to the nonnormal distribution of the data. To account for missing data, the last observation carried forward (LOCF) technique was used. We analyzed the change difference of the minimum FCT with a linear mixed-effects model, which included the fixed effects of treatment group and baseline FCT value, with a random intercept for study center to account for variability between sites. Furthermore, as a sensitivity analysis, we included the change in LDL-C from baseline to the 12-month follow-up time point as a covariate in the model. To test the robustness of our findings against missing data due to loss to follow-up, we performed multiple imputation under the assumption of MAR and a series of scenarios for MNAR using delta-adjusted multiple imputation.

For safety variables, we applied descriptive statistics for all patients who were randomized and received at least one dose of the study drug. All treatment-emergent adverse events were recorded, and the rates of adverse events were summarized.

Statistical analyses adhered to the prespecified plan (Supplementary Materials IV), and all statistical analyses were performed using SAS software (version 9.4). Two-sided $P < 0.05$ denoted statistical significance.

DATA AVAILABILITY

The protocol, statistical analysis plan, and other relevant study materials of this research have been made publicly available online. The raw data supporting the

results of this article have been deposited in the Clinical Trial Management Public Platform (http://www.medresman.org.cn; No. ChiCTR1900025842).

ACKNOWLEDGEMENTS

This work was funded by grants from the National Key Research and Development Program of China (2017YFC1700502-P.B.), the National Natural Science Foundation of China (82430015-Y.Z., 82241203-C.Z., 82030051-Y.Z., 82270257-P.B.), the Key R&D Program of Shandong Province (2021SFGC0503-Y.Z., 2021ZLGX02-C.Z.), the State Key R&D Program of China (2021YFF0501403-C.Z.), and the Taishan Scholars Program of Shandong Province (C.Z.). We thank all the site teams and participants for their contributions to the trial; Wenqiang Chen (Department of Cardiology, Qilu Hospital of Shandong University, Jinan, China), Guipeng An (Department of Cardiology, Qilu Hospital of Shandong University, Jinan, China), Jianmin Yang (Department of Cardiology, Qilu Hospital of Shandong University, Jinan, China), Xi Su (Department of Cardiology, Wuhan Asia Heart Hospital, Wuhan, China), Jianqiang Peng (Department of Cardiology, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, China), Bo Zhang (Department of Cardiology, The First Affiliated Hospital of Dalian Medical University, Dalian, China), Jun Xiao (Department of Cardiology, Chongqing University Central Hospital, Chongqing Emergency Medical Center, The Fourth People's Hospital of Chongqing, Chongqing, China), Zengming Xue (Department of Cardiology, Langfang People's Hospital, Langfang, China) and Jianhong Tao (Department of Cardiology, Sichuan Provincial People's Hospital, Chengdu, China) for their help with data collection and patient follow-up; Xiaoyan Yan (Department of Biostatistics, Peking University Clinical Research Institute, Peking University First Hospital, Beijing, China), Meixia Shang (Department of Biostatistics, Peking University Clinical Research Institute, Peking University First Hospital, Beijing, China) and Yuxin Ding (Department of Biostatistics, Peking University Clinical Research Institute, Peking University First Hospital, Beijing, China) for their help with statistical analysis; and Guo Wei (Department of Cardiology, The Second Affiliated Hospital of Harbin Medical University, Harbin, China) and Yanchao Liu (Department of Cardiology, The Second Affiliated Hospital of Harbin Medical University, Harbin, China) for their help with OCT image analysis.

AUTHOR CONTRIBUTIONS

Cheng Zhang, Peili Bu, Yun Zhang, and Bo Yu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Mei Ni, Yun Ti, and Huai Yu contributed equally to this article. Concept and design: Peili Bu, Yun Zhang and Cheng Zhang; Acquisition, analysis, or interpretation of data: Mei Ni, Yun Ti, Huai Yu, Bo Yu, Yun Zhang, Peili Bu and Cheng Zhang; Drafting of the manuscript: Peili Bu, Yun Zhang and Cheng Zhang; Critical review of the manuscript for important intellectual content: Mei Ni, Yun Ti, Huai Yu, Meng Zhang, Yan Qi, Dayue Darrel Duan, Qiang Xie, Zheng Ji, Ranzun Zhao, Yujie Zhou, Shaoliang Chen, Lin Wang, Yaojun Zhang, Jincheng Guo, Yuquan He, Bo Yu, Peili Bu, Yun Zhang and Cheng Zhang; Statistical analysis: Chen Yao; Obtained funding: Peili Bu; Administrative, technical, or material support: Huai Yu, Meng Zhang, Yan Qi, Dayue Darrel Duan, Qiang Xie, Zheng Ji, Ranzun Zhao, Yujie Zhou, Shaoliang Chen, Lin Wang, Yaojun Zhang, Jincheng Guo, Yuquan He and Bo Yu. Supervision: Peili Bu, Yun Zhang and Cheng Zhang. All authors have read and approved the article.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41392-026-02581-z.

Competing interests: The authors declare no competing interests.

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