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Traditional Chinese Medicine Compound (Tongxinluo) and Clinical Outcomes of Patients With Acute Myocardial Infarction
The CTS-AMI Randomized Clinical Trial

Yuejin Yang, MD, PhD; Xiangdong Li, MD, PhD; Guihao Chen, MD, PhD; Ying Xian, MD, PhD; Haitao Zhang, MD, PhD; Yuan Wu, MD; Yanmin Yang, MD; Jianhua Wu, MD; Chuntong Wang, MD; Shenghu He, MD; Zhong Wang, MD; Yixin Wang, MD; Zhifang Wang, MD; Hui Liu, MD; Xiping Wang, MD; Minzhou Zhang, MD; Jun Zhang, MD, PhD; Jia Li, MD; Tao An, MD; Hao Guan, MD; Lin Li, MD; Meixia Shang, MD; Chen Yao, MD; Yaling Han, MD, PhD; Boli Zhang, MD; Runlin Gao, MD; Eric D. Peterson, MD, MPH; for the CTS-AMI Investigators

IMPORTANCE Tongxinluo, a traditional Chinese medicine compound, has shown promise in in vitro, animal, and small human studies for myocardial infarction, but has not been rigorously evaluated in large randomized clinical trials.

OBJECTIVE To investigate whether Tongxinluo could improve clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI).

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled clinical trial was conducted among patients with STEMI within 24 hours of symptom onset from 124 hospitals in China. Patients were enrolled from May 2019 to December 2020; the last date of follow-up was December 15, 2021.

INTERVENTIONS Patients were randomized 1:1 to receive either Tongxinluo or placebo orally for 12 months (a loading dose of 2.08 g after randomization, followed by the maintenance dose of 1.04 g, 3 times a day), in addition to STEMI guideline-directed treatments.

MAIN OUTCOMES AND MEASURES The primary end point was 30-day major adverse cardiac and cerebrovascular events (MACCEs), a composite of cardiac death, myocardial reinfarction, emergent coronary revascularization, and stroke. Follow-up for MACCEs occurred every 3 months to 1 year.

RESULTS Among 3797 patients who were randomized, 3777 (Tongxinluo: 1889 and placebo: 1888; mean age, 61 years; 76.9% male) were included in the primary analysis. Thirty-day MACCEs occurred in 64 patients (3.4%) in the Tongxinluo group vs 99 patients (5.2%) in the control group (relative risk [RR], 0.64 [95% CI, 0.47 to 0.88]; risk difference [RD], −1.8% [95% CI, −3.2% to −0.6%]). Individual components of 30-day MACCEs, including cardiac death (56 [3.0%] vs 80 [4.2%]; RR, 0.70 [95% CI, 0.50 to 0.99]; RD, −1.2% [95% CI, −2.5% to −0.1%]), were also significantly lower in the Tongxinluo group than the placebo group. By 1 year, the Tongxinluo group continued to have lower rates of MACCEs (100 [5.3%] vs 157 [8.3%]; HR, 0.64 [95% CI, 0.49 to 0.82]; RD, −3.0% [95% CI, −4.6% to −1.4%]) and cardiac death (85 [4.5%] vs 116 [6.1%]; HR, 0.73 [95% CI, 0.55 to 0.97]; RD, −1.6% [95% CI, −3.1% to −0.2%]). There were no significant differences in other secondary end points including 30-day stroke; major bleeding at 30 days and 1 year; 1-year all-cause mortality; and in-stent thrombosis (<24 hours; 1-30 days; 1-12 months). More adverse drug reactions occurred in the Tongxinluo group than the placebo group (40 [2.1%] vs 21 [1.1%]; $P = .02$), mainly driven by gastrointestinal symptoms.

CONCLUSIONS AND RELEVANCE In patients with STEMI, the Chinese patent medicine Tongxinluo, as an adjunctive therapy in addition to STEMI guideline-directed treatments, significantly improved both 30-day and 1-year clinical outcomes. Further research is needed to determine the mechanism of action of Tongxinluo in STEMI.

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Visual Abstract

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The CTS-AMI Investigators appear listed in Supplement 4.

Corresponding Authors: Yuejin Yang, MD, PhD (yangyjfw@126.com), and Runlin Gao, MD (gaorunlin@citmd.com), State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 BeiLishi Rd, Xicheng District, Beijing 100037, China.

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Acute ST-segment elevation myocardial infarction (STEMI) is a major life-threatening condition worldwide.[1] Despite reperfusion therapy and optimal medical management, patients with STEMI still face high risks of in-hospital mortality and recurrent cardiovascular events.[1-3]

Tongxinluo, a traditional Chinese medicine compound, is composed of powders and extracts from multiple plant and insect products.[4,5] Although the active ingredient(s) and the exact mechanism of action remain unclear, it has been suggested that peoniflorin,[6] ginsenoside Rg1,[7,8] and ginsenoside Rb1[9] present in Tongxinluo have potential cardioprotective effects. Tongxinluo was initially evaluated and approved in China for angina pectoris and ischemic stroke in 1996.[4] Tongxinluo pretreatment was found in vitro to directly reduce endothelial cell apoptosis via autophagy induction.[10] Tongxinluo could also reduce hypoxia/reoxygenation-induced injury of cardiomyocytes,[11] alleviate myocardial ischemic/reperfusion injury via the activation of nitric oxide synthase[12] and stimulate proangiogenesis after coronary permanent ligation in rats.[13] Prior swine studies have demonstrated that pretreating with Tongxinluo for 3 days,[14] 3 hours,[15] or 1 hour[16] before myocardial infarction (MI) facilitated myocardial microvascular perfusion and reduced infarcted area after reperfusion.[16,17] Furthermore, a multicenter, randomized, double-blind, placebo-controlled clinical trial found Tongxinluo significantly promoted myocardial microvascular perfusion in 108 patients with STEMI treated with primary percutaneous coronary intervention (PCI).[18] Based on these in vitro, animal, and small human studies, it was hypothesized that Tongxinluo may improve clinical outcomes in patients with STEMI.[19]

Key Points

Question Among patients with acute ST-segment elevation myocardial infarction (STEMI), does the addition of a traditional Chinese medicine compound (Tongxinluo) as an adjunctive treatment to guideline-directed therapies improve clinical outcomes?

Findings In this randomized, double-blind, placebo-controlled clinical trial of 3777 patients with STEMI, oral administration of Tongxinluo for 12 months, compared with placebo, significantly reduced the primary end point of 30-day major adverse cardiac and cerebrovascular events (rate of MACCEs, 3.4% vs 5.2%), with a significant reduction in cardiac death (3.0% vs 4.2%). These benefits persisted within 1 year (MACCEs: 5.3% vs 8.3%; cardiac death: 4.5% vs 6.1%), with no significant difference in major bleeding.

Meaning Among patients with STEMI, Tongxinluo improved both 30-day and 1-year clinical outcomes.

Methods

Study Design and Oversight

The China Tongxinluo Study for Myocardial Protection in Patients With Acute Myocardial Infarction (CTS-AMI) was a randomized, double-blind, placebo-controlled, multicenter clinical trial conducted in 124 clinical centers in China. Details regarding the trial design have been described previously[19] and a copy of the study protocol (version 2.0) and statistical analysis plan (SAP version 3.0) are available in Supplement 1. This trial was designed and coordinated by the authors and overseen by a steering committee and a data and safety monitoring board. Patients were randomized 1:1 to receive either Tongxinluo or placebo, in addition to STEMI guideline-directed treatments. Ethics approval was obtained from the ethics committees at each study site. This study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Study Population

Patients were eligible for enrollment if they were 18 years or older and presented within 24 hours of symptom onset with an acute myocardial infarction, with ST-segment elevation of 0.2 mV or greater in more than 2 adjacent leads or new left bundle-branch block. Exclusion criteria included severe complications of STEMI, such as mechanical complications, serious cardiogenic shock not responding to vasopressors, uncontrolled acute left-sided heart failure or pulmonary edema, and malignant arrhythmias uncontrolled by antiarrhythmia agents at enrollment, and severe comorbidities, such as severe hepatic dysfunction, severe kidney dysfunction, severe infection, bleeding tendency, malignancies, and life expectancy of less than 1 year. The complete exclusion criteria are listed in the study protocol in Supplement 1. Written informed consent was provided by all patients or their legal representatives before randomization.

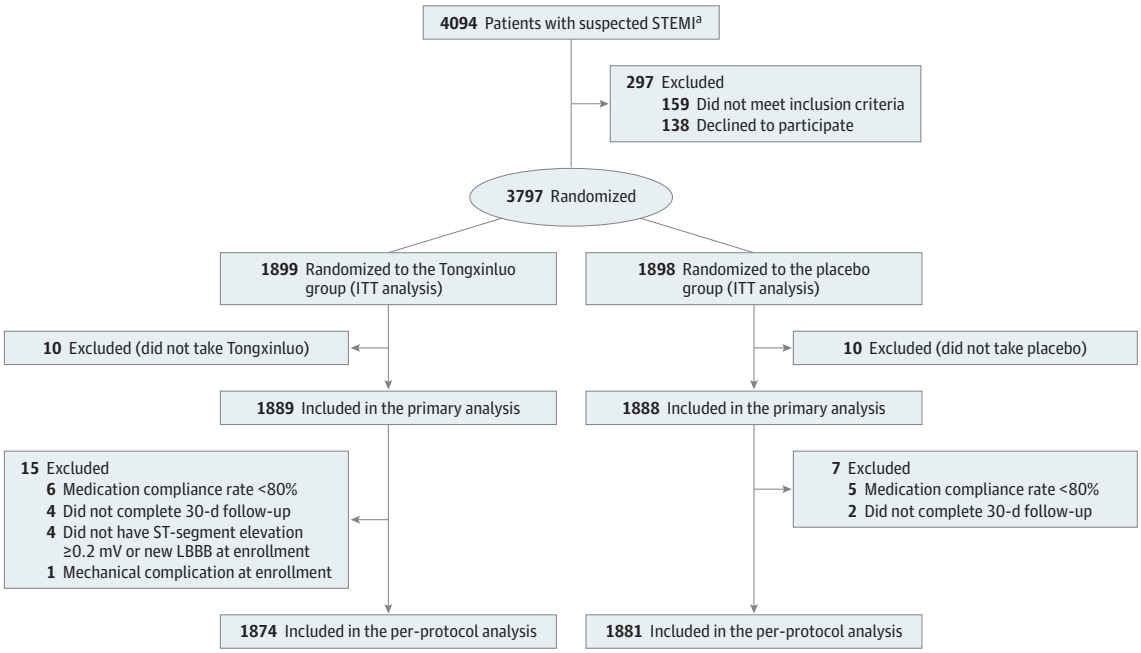
Randomization and Blinding

Patients were assigned to Tongxinluo or placebo at a 1:1 ratio (block randomization stratified by site), with a randomizing number automatically generated in a computer-based central randomization system (Peking University Clinical Research Institute, Beijing, China) (**Figure 1**). Each randomizing number was automatically and double-blindingly bound with the package number of research drugs (Tongxinluo or placebo). Before drug distribution, investigators applied for the corresponding research drug with the randomizing number via the system. All participants involved in this trial, including the patients, physicians, nurses, site investigators, and members of the clinical end point committee, were blinded to the treatment assignments.

Procedures

Patients in the Tongxinluo group were treated with an oral loading dose of Tongxinluo (8 capsules, 2.08 g) after randomization, followed by the maintenance dose of 4 capsules (1.04 g), 3 times a day for 12 months. More information about Tongxinluo, such as compound preparation, is provided in section 1.1.1 in Supplement 2. The placebo group received matching placebo capsules, specifically developed for the Tongxinluo trial (see section 1.1.2 in Supplement 2). The placebo capsule had the same appearance as the Tongxinluo capsule, with similar taste and odor if the capsule was opened. Treating physicians were instructed to provide

Figure 1. Population Included in the CTS-AMI Study



CTS-AMI indicates China Tongxinluo Study for Myocardial Protection in Patients With Acute Myocardial Infarction; ITT, intention to treat; LBBB, left bundle-branch block; and STEMI, ST-segment elevation myocardial infarction.

[a] Due to the emergent circumstances surrounding patient enrollment and randomization amid the COVID-19 pandemic, screening logs were only available in 82 of 124 sites. As a result, the exact number of potentially eligible patients screened were not known, but it was estimated to be around 50 patients per site in sites with complete screening logs.

STEMI guideline-directed treatments including dual antiplatelet therapy and coronary reperfusion (primary PCI or thrombolysis, unless contraindicated or declined by the patients, their family members, and interventional cardiologists).[20,21] Usage of thrombus aspiration catheter, distal protective devices, platelet glycoprotein IIb/IIIa receptor antagonist, and stent implantation during primary PCI was at the discretion of the interventionalists.

Baseline characteristics of each patient's clinical presentation (**Table 1**), electrocardiogram (ECG), and laboratory tests were collected at admission. ECG was also taken at 2 hours, 24 hours, and 7 days after admission/reperfusion therapy. Additional laboratory tests, echocardiogram, 24-hour dynamic ECG (Holter monitor), and elective PCI, if indicated, were scheduled on the seventh day of hospitalization or before discharge. All surviving patients were followed up for 1 year, with follow-up visits scheduled at 1, 3, 6, 9, and 12 months (study schedule and study schedule flowchart are in Supplement 1). ECG, coronary angiography, and echocardiography data were reviewed and verified by each corresponding independent core laboratory on a random sample of 33% of patients recruited in this trial for checking the rates of consistency (eTable 1 in Supplement 3).

Outcomes

The primary end point was a composite of the major adverse cardiac and cerebrovascular events (MACCEs) at 30 days, which included cardiac death, myocardial reinfarction, emergent coronary revascularization, and stroke. Secondary end points included individual components of the primary end point; severe complications of STEMI comprising cardiogenic shock, acute left heart failure, mechanical complications, and malignant arrhythmias at 30 days; major bleeding (Bleeding Academic Research Consortium grades III and V) at 30 days and 12 months; MACCEs, rehospitalization due to heart failure, and all-cause mortality at 1 year; in-stent thrombosis (<24 h; 1-30 days; 1-12 months); and the evaluation of myocardial reperfusion with the resolution of elevated ST-segment and incidence of no reflow at 2 hours, 24 hours, and 7 days after reperfusion therapy. ST-segment resolution was calculated as the difference value of ST-segment elevation in the most elevated lead in ECG (mean value of 3 ST consecutive cardiac cycles) between baseline and postreperfusion time points (2 hours, 24 hours, or 7 days). Myocardial no reflow was defined as ST-segment resolution of 50% or less of baseline at 2 hours after reperfusion therapy or 75% or less of baseline at 24 hours or 7 days after reperfusion therapy. All end point events were reviewed by an independent clinical end point committee (see section 1.2 in Supplement 2), whose members were blinded to the research group assignments. Definitions for each outcome are listed in section 1.3 of Supplement 2.

Statistical Analysis

Assuming a 30-day MACCE rate of 9% in the placebo group and 6.3% in the Tongxinluo group based on previous reports

Table 1. Baseline Characteristics of the Study Population

	No. (%)	
	Tongxinluo (n = 1889)	Placebo (n = 1888)
Baseline characteristics		
Age, mean (SD), y	61.4 (12.1)	61.5 (12.1)
Age group		
<60 y	807 (42.7)	795 (42.1)
60-75 y	850 (45.0)	859 (45.5)
>75 y	232 (12.3)	234 (12.4)
Sex		
Male	1456 (77.1)	1448 (76.7)
Female	433 (22.9)	440 (23.3)
Body mass index, mean (SD)[a]	24.5 (3.0)	24.5 (3.0)
Risk factors		
Hypertension	948 (50.2)	959 (50.8)
Current smoking	828 (43.8)	790 (41.8)
Dyslipidemia	454 (24.0)	452 (23.9)
Diabetes	418 (22.1)	398 (21.1)
Medical history		
Angina pectoris	513 (27.2)	537 (28.4)
Stroke	174 (9.2)	187 (9.9)
Revascularization therapy	98 (5.2)	108 (5.7)
PCI	96 (5.1)	105 (5.6)
CABG	3 (0.2)	4 (0.2)
Myocardial infarction	88 (4.7)	111 (5.9)
Heart failure	10 (0.5)	12 (0.6)
Presentation features		
Onset-to-arrival time, median (IQR), h	2.7 (1.4-5.2)	2.9 (1.5-5.3)
<6	1485 (78.6)	1473 (78.0)
6-12	277 (14.7)	276 (14.6)
>12	127 (6.7)	139 (7.4)
Systolic blood pressure, mean (SD), mm Hg	131.5 (24.6)	132.4 (24.2)
<90 mm Hg	56 (3.0)	46 (2.4)
≥140 mm Hg	680 (36.0)	683 (36.2)
Diastolic blood pressure, mean (SD), mm Hg	81.9 (16.0)	81.8 (16.0)
<60 mm Hg	108 (5.7)	108 (5.7)
≥90 mm Hg	576 (30.5)	592 (31.4)
Heart rate, mean (SD), beats/min	75.2 (16.9)	75.6 (17.1)
Infarct location		
Anterior	794 (42.0)	809 (42.8)
Inferior	737 (39.0)	759 (40.2)
Lateral	47 (2.5)	28 (1.5)
Posterior	7 (0.4)	8 (0.4)
Other[b]	304 (16.1)	284 (15.0)
Killip class at admission[c]		
I (None)	1715 (90.8)	1708 (90.5)
II	133 (7.0)	135 (7.2)
III	14 (0.7)	21 (1.1)
IV (Cardiogenic shock)	27 (1.4)	24 (1.3)
Arrhythmia detected by ECG or telemetry monitor on admission and prior to intervention		
Ventricular tachycardia	12 (0.6)	5 (0.3)
Ventricular fibrillation	23 (1.2)	18 (1.0)
New-onset atrial fibrillation/flutter	35 (1.9)	24 (1.3)
Second- (type 2) or third-degree AV block	37 (2.0)	36 (1.9)

(continued)

Table 1. Baseline Characteristics of the Study Population (continued)

	No. (%)	
	Tongxinluo (n = 1889)	Placebo (n = 1888)
LVEF assessed after randomization, reperfusion, or medical therapy, median (IQR), %	57.0 (51.0-61.0) [n = 1751]	56.0 (50.1-61.0) [n = 1721]
CK-MB peak level in the first 24 h, median (IQR), U/L	91.3 (37.2-179.1) [n = 1535]	92.0 (38.0-180.4) [n = 1543]
Hospital characteristics[d]		
Province level	233 (12.3)	248 (13.1)
Prefecture level	1121 (59.3)	1115 (59.1)
County level	535 (28.3)	525 (27.8)

Abbreviations: AV, atrioventricular; CABG, coronary artery bypass grafting; CK-MB, creatine kinase-MB; ECG, electrocardiogram; IQR, interquartile range; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Including those who have more than 1 infarction location, as shown by ECG.

[c] Killip class I indicates no clinical signs of heart failure (free of rales and a third heart sound [S3]); II, rales in the lungs, but only to a mild to moderate degree (<50% of lung fields), and may or may not have an S3; III, rales in more than half of each lung field or have pulmonary edema; and IV, cardiogenic shock.

[d] A province-level hospital is similar to a tertiary hospital in the US that is a comprehensive, referral hospital serving as a hub to all regions in the province. A prefecture-level hospital is similar to a large regional hospital in the US providing comprehensive health services on a regional basis. A county-level hospital is the one affiliated with a county and contains much fewer beds and resources than a prefecture- or province-level hospital.

and an estimated dropout rate of 20%,[19,22,23] a total of 1898 patients would be required in each group (80% power, 2-sided α = .05 and β = 0.20). The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Continuous variables were presented as means (SDs) or medians (IQRs), and intergroup comparisons were performed using the 2-tailed *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables were analyzed using χ^2 test or Fisher exact test and were presented as frequencies and percentages.

We reported the incidence rate of 30-day MACCEs (primary end point) for each group, along with adjusted risk ratios (RRs) and risk differences (RDs) using a Cochran-Mantel-Haenszel test, considering center as a randomization stratification factor. Similar methods were also used for other 30-day end points between the Tongxinluo and placebo groups. In addition, we used forest plots to assess treatment heterogeneity of 30-day MACCEs for prespecified subgroups (SAP in Supplement 1). Exploratory subgroup analysis was performed based on onset-to-arrival time (≤12 hours, >12 hours) and serum creatinine level at admission (≤0.5 or >0.5 upper limit of normal). For 1-year end points, we compared Tongxinluo and placebo groups using Cox proportional hazard model and reported adjusted hazard ratios (HRs) and RDs. A post hoc landmark analysis was also performed at the 30-day landmark point for the 1-year MACCEs. The incidences of adverse events and serious adverse events were analyzed and compared between the 2 groups using the χ^2 test or Fisher exact test.

The primary analysis included all randomized participants except for those who had not taken the study drugs after randomization or did not have any data after randomization (n = 10 in the Tongxinluo group and n = 10 in the placebo group).[24] We also performed analyses in the intention-to-treat (all randomized participants) and per-protocol (excluding those who had major protocol deviation[s], did not complete 30-day follow-up, or did not complete the pre-set minimal exposure to the assigned study drug [at least 80% adherence]) populations. According to the prespecified SAP, missing values in the primary end point of 30-day MACCEs were imputed as having an event prior to unblinding. Sensitivity analyses were also performed by imputing missing value to no event in both the Tongxinluo and placebo groups or imputing to event in the Tongxinluo group but no event in the placebo group as the most conservative approach.

A 2-sided $P < .05$ was considered statistically significant unless otherwise specified. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute) by Peking University Clinical Research Institute. Full details of the statistical methods are available in the SAP in Supplement 1. Additionally, study data were reanalyzed by an independent third-party company (Tigermed) to double-check the results of this trial (see section 1.4 in Supplement 2).

Results

Between May 23, 2019, and December 8, 2020, a total of 3797 patients were enrolled from 124 hospitals in China, with 1899 patients assigned to the Tongxinluo group and 1898 to the placebo group (intention-to-treat analysis, Figure 1). Among them, 20 patients did not take the study drugs (10 in the Tongxinluo and 10 in the placebo group), leaving 3777 patients (1889 in the Tongxinluo group and 1888 in the placebo group) for the primary analysis. A total of 22 patients (15 in the Tongxinluo and 7 in the placebo group) were excluded from the confirmatory per-protocol analysis. Among them, 4 patients in the Tongxinluo and 2 in the placebo group did not complete 30-day follow-up. According to the SAP, these patients' primary end point of 30-day MACCEs were imputed as having an event in the primary analysis population. The last date of follow-up was December 15, 2021.

Characteristics and Care Management of Patients

Both the Tongxinluo and placebo groups were well balanced with respect to patient baseline characteristics and care details (Tables 1 and 2). The mean age of participants was 61 years and 76.9% were male. Most patients had lower

Table 2. Care Management of the Study Population

	No. (%)	
	Tongxinluo (n = 1889)	Placebo (n = 1888)
Medications during hospitalization		
P2Y12 receptor inhibitors	1881 (99.6)	1876 (99.4)
Ticagrelor	1286 (68.1)	1287 (68.2)
Clopidogrel	595 (31.5)	589 (31.2)
Aspirin	1879 (99.5)	1873 (99.2)
Statins	1824 (96.6)	1811 (95.9)
Nitrates	1441 (76.3)	1431 (75.8)
β-Blockers	1205 (63.8)	1201 (63.6)
ACEIs or ARBs (ARNI included)	1028 (54.4)	1082 (57.3)
Diuretics (excluding spironolactone)	523 (27.7)	532 (28.2)
Spironolactone	418 (22.1)	416 (22.0)
SGLT2 inhibitors	37 (2.0)	23 (1.2)
Procedural details		
Coronary angiography	1730 (91.6)	1680 (89.0)
No. of vessels with substantial stenosis (≥50%)		
1	611 (35.3)	542 (32.3)
2	452 (26.1)	488 (29.1)
3	659 (38.1)	642 (38.2)
Left main coronary artery	8 (0.5)	8 (0.5)
Infarct-related coronary artery		
Left anterior descending	803 (46.4)	770 (45.8)
Left main coronary	8 (0.5)	15 (0.9)
Other	919 (53.1)	896 (53.3)
Reperfusion therapy	1656 (87.7)	1629 (86.3)
Primary PCI	1560 (82.6)	1504 (79.7)
Symptom-to-balloon time, median (IQR), h	4.2 (2.7-7.1)	4.3 (2.8-7.1)
Door-to-balloon time, median (IQR), min	76 (55-110)	75 (55-110)
Stenting of culprit lesion by primary PCI	1488 (95.4)	1415 (94.1)
TIMI flow grade before PCI		
0/1	1221/1485 (82.2)	1168/1411 (82.8)
2	120/1485 (8.1)	107/1411 (7.6)
3	144/1485 (9.7)	136/1411 (9.6)
TIMI flow grade after PCI		
0/1	0	6 (0.4)
2	0	1 (0.1)
3	1485/1485 (100)	1404/1411 (99.5)
Thrombolysis	95 (5.0)	123 (6.5)
Symptom-to-needle time, median (IQR), h	2.8 (1.9-5.2)	3.3 (2.0-4.8)
Door-to-needle time, median (IQR), min	44 (31-73) [n = 93]	55 (30-89) [n = 118]
Thrombolysis + rescue PCI	52 (54.7)	68 (55.3)
CABG	1 (0.1)	2 (0.1)
Elective PCI before discharge	189 (10.0)	221 (11.7)
Discharge medications		
P2Y12 receptor inhibitors	1787 (94.6)	1760 (93.2)
Ticagrelor	1018 (53.9)	1014 (53.7)
Clopidogrel	769 (40.7)	746 (39.5)
Aspirin	1784 (94.4)	1757 (93.1)
Statins	1758 (93.1)	1726 (91.4)
β-Blockers	1096 (58.0)	1057 (56.0)
ACEIs or ARBs (ARNI included)	918 (48.6)	955 (50.6)
Nitrates	768 (40.7)	727 (38.5)
Spironolactone	305 (16.2)	303 (16.1)
Diuretics (excluding spironolactone)	298 (15.8)	288 (15.3)
SGLT2 inhibitors	37 (2.0)	23 (1.2)
Length of hospital stay, median (IQR), d	9 (8-12)	9 (7-12)

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ARNI, angiotensin receptor–neprilysin inhibitor; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SGLT2, sodium-glucose cotransporter 2; TIMI, Thrombolysis in Myocardial Infarction.

Table 3. Primary and Secondary Outcomes

Outcome	No. (%)		RD (95% CI), %	RR[a] or HR[b] (95% CI)	*P* value
	Tongxinluo (n = 1889)	Placebo (n = 1888)			
Primary outcome					
30-d MACCEs[c]	64 (3.4)	99 (5.2)	−1.8 (−3.2 to −0.6)	0.64 (0.47 to 0.88)	.006
Secondary outcomes					
Individual components of 30-d MACCEs					
Cardiac death	56 (3.0)	80 (4.2)	−1.2 (−2.5 to −0.1)	0.70 (0.50 to 0.99)	.04
Myocardial reinfarction	0	9 (0.5)	−0.5 (−0.8 to −0.2)	0.35 (0.13 to 0.99)	.003
Emergent coronary revascularization	0	0			
Stroke	4 (0.2)	9 (0.5)	−0.3 (−0.7 to 0.1)	0.44 (0.14 to 1.43)	.16
30-d Severe STEMI complications	221 (11.8)	277 (14.8)	−3.0 (−5.2 to −0.8)	0.80 (0.68 to 0.94)	.008
Cardiogenic shock	44 (2.4)	61 (3.3)	−0.9 (−2.0 to 0.1)	0.71 (0.48 to 1.05)	.08
Acute left-sided heart failure	42 (2.3)	43 (2.4)	−0.1 (−1.1 to 0.9)	1.06 (0.70 to 1.60)	.78
Malignant arrhythmias	144 (7.8)	186 (10.2)	−2.4 (−4.2 to −0.5)	0.77 (0.62 to 0.94)	.01
Mechanical complications	10 (0.5)	13 (0.7)	−0.2 (−0.7 to 0.3)	0.77 (0.34 to 1.75)	.53
30-d Major bleeding	8 (0.4)	13 (0.7)	−0.3 (−0.8 to 0.2)	0.58 (0.24 to 1.43)	.23
1-y Major bleeding	13 (0.7)	19 (1.0)	−0.3 (−0.9 to 0.3)	0.66 (0.32 to 1.35)	.25
1-y MACCEs	100 (5.3)	157 (8.3)	−3.0 (−4.6 to −1.4)	0.64 (0.49 to 0.82)	<.001
Cardiac death	85 (4.5)	116 (6.1)	−1.6 (−3.1 to −0.2)	0.73 (0.55 to 0.97)	.03
Myocardial reinfarction	6 (0.3)	21 (1.1)	−0.8 (−1.3 to −0.3)	0.26 (0.10 to 0.67)	.005
Emergent coronary revascularization	0	0			
Stroke	10 (0.5)	24 (1.3)	−0.8 (−1.3 to −0.1)	0.44 (0.21 to 0.92)	.03
1-y Rehospitalization due to heart failure	16 (0.9)	35 (1.9)	−1.0 (−1.7 to −0.3)	0.48 (0.26 to 0.87)	.02
1-y All-cause death	97 (5.1)	124 (6.6)	−1.5 (−2.9 to 0.1)	0.77 (0.59 to 1.01)	.06
In-stent thrombosis	10 (0.5)	11 (0.6)	−0.1 (−0.5 to 0.4)	0.96 (0.40 to 2.27)	.92
Acute: <24 h	0	0			
Subacute: 1-30 d	2 (0.1)	3 (0.2)	−0.1 (−0.3 to 0.2)	0.59 (0.09 to 3.94)	.59
Late: 1-12 mo	8 (0.4)	8 (0.4)	−0.0 (−0.4 to 0.4)	1.09 (0.41 to 2.86)	.87
ST-segment resolution, mV[d]					
2 h after reperfusion therapy					
Mean (SD)	−0.21 (0.19)	−0.21 (0.19)	0.00 (−0.01 to 0.01)		
Median (IQR)	−0.20 (−0.30 to −0.10)	−0.20 (−0.30 to −0.10)			.90
24 h after reperfusion therapy					
Mean (SD)	−0.26 (0.19)	−0.24 (0.19)	−0.02 (−0.03 to −0.01)		
Median (IQR)	−0.20 (−0.30 to −0.15)	−0.20 (−0.30 to −0.10)			.01
7 d after reperfusion therapy					
Mean (SD)	−0.30 (0.19)	−0.30 (0.19)	0.00 (−0.01 to 0.02)		
Median (IQR)	−0.20 (−0.40 to −0.20)	−0.25 (−0.40 to −0.20)			.38
Myocardial no reflow in ECG					
2 h after reperfusion therapy	418 (27.8)	402 (27.4)	0.4 (−2.8 to 3.6)	1.01 (0.90 to 1.13)	.90
24 h after reperfusion therapy	664 (45.2)	678 (48.1)	−2.9 (−6.5 to 0.8)	0.93 (0.86 to 1.01)	.08
7 d after reperfusion therapy	356 (27.9)	349 (27.7)	0.2 (−3.3 to 3.6)	1.00 (0.89 to 1.14)	.95

Abbreviations: ECG, electrocardiogram; HR, hazard ratio; MACCEs, major adverse cardiac and cerebrovascular events; RD, risk difference; RR, relative risk; STEMI, ST-segment elevation myocardial infarction.

[a] RR for 30-day outcomes.

[b] HR for 1-year outcomes.

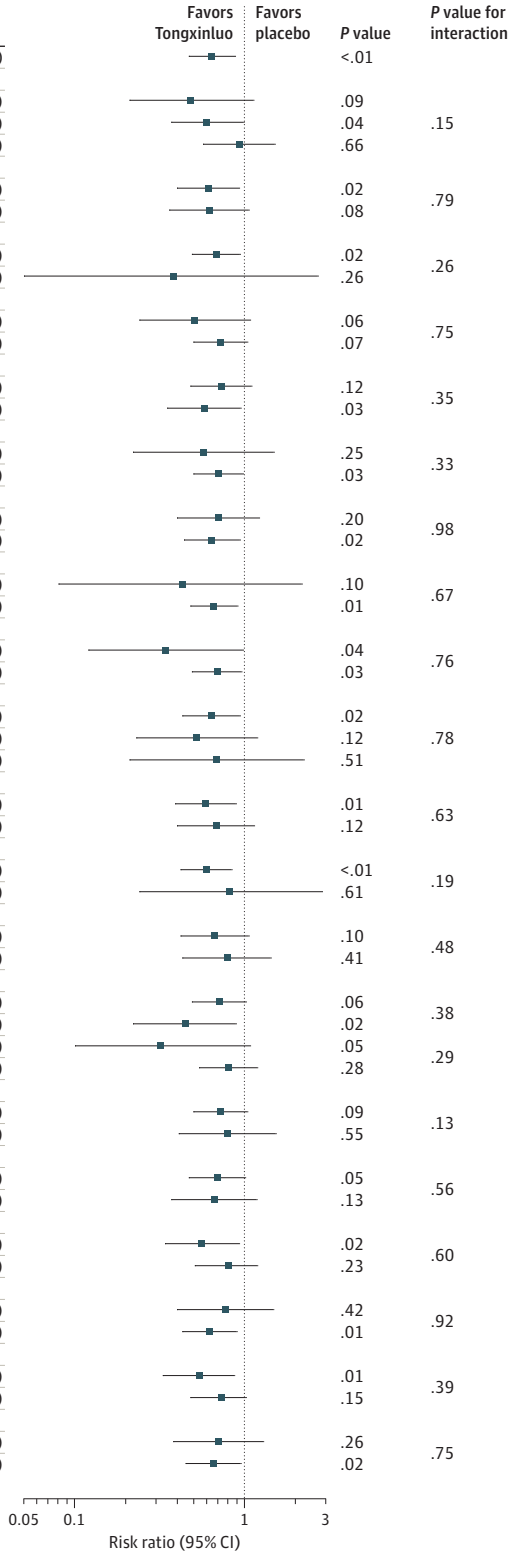
[c] According to the prespecified statistical analysis plan, 4 patients in the Tongxinluo group and 2 patients in the placebo group who did not complete 30-day follow-up with missing value in the primary end point of 30-day MACCEs were imputed as having an event. MACCEs are a composite of cardiac death, myocardial reinfarction, emergent coronary revascularization, and stroke.

[d] ST-segment resolution was calculated as the difference value of ST-segment elevation in the most elevated lead in ECG (mean value of 3 ST consecutive cardiac cycles) between baseline and postreperfusion time points (2 hours, 24 hours, or 7 days). Myocardial no reflow was defined as ST-segment resolution ≤50% of baseline at 2 hours after reperfusion therapy or ≤75% of baseline at 24 hours or at 7 days after reperfusion therapy.

Killip class at admission (class I: 90.6%; class II: 7.1%). Nearly all patients received aspirin, P2Y12 receptor inhibitors, and statins, while less than two-thirds of patients received β-blockers and about half of patients received angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) during hospitalization (Table 2). These

Figure 2. Subgroup Analysis for the Primary End Point of 30-Day Major Adverse Cardiac and Cerebrovascular Events

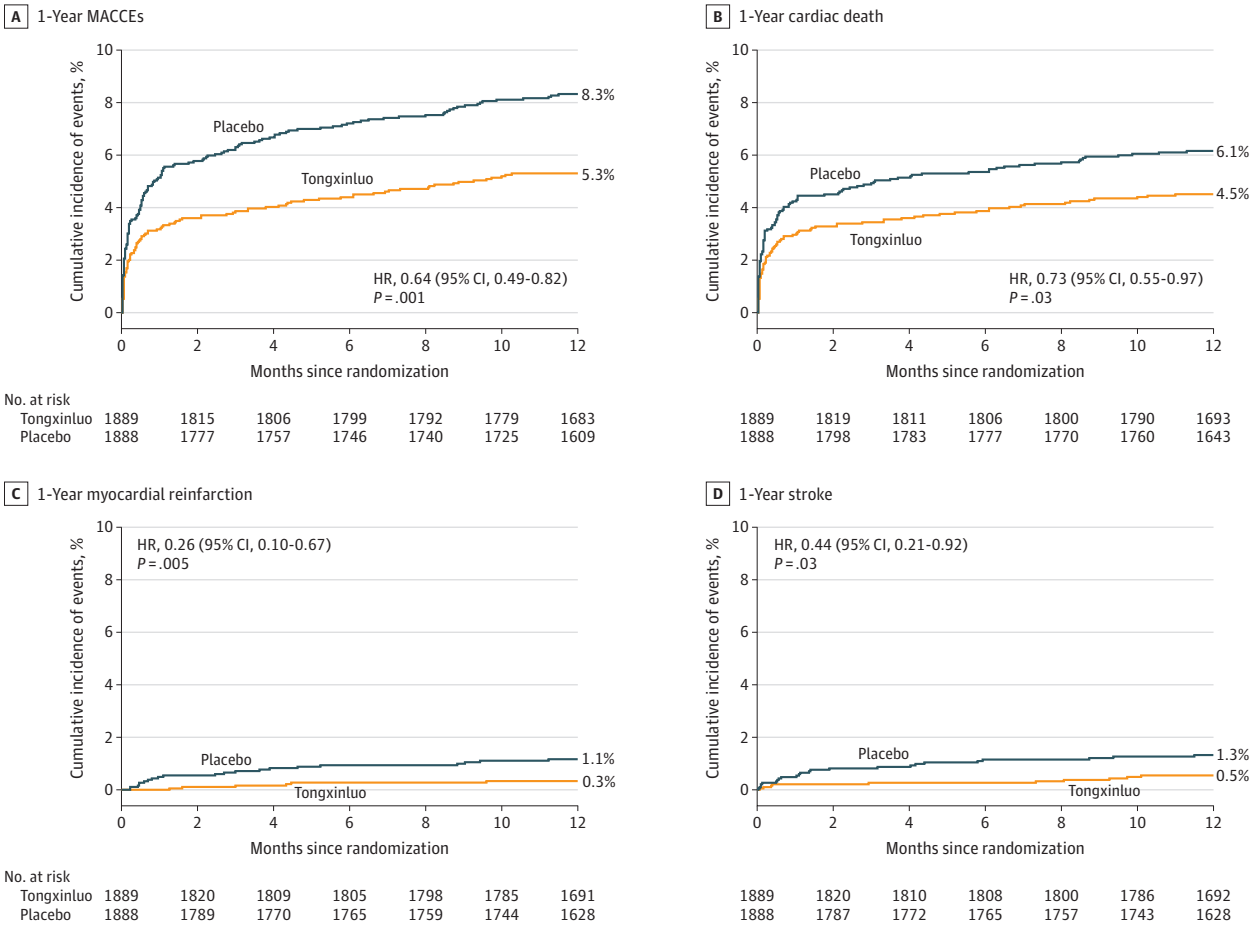
Subgroup	No. of events/ total No.		Risk ratio (95% CI)	*P* value	*P* value for interaction
	Tongxinluo	Placebo			
Overall			0.64 (0.47-0.88)	<.01	
Age, y					
<60	7/807	17/795	0.48 (0.21-1.13)	.09	
60-75	28/850	47/859	0.60 (0.37-0.99)	.04	.15
>75	29/232	35/234	0.93 (0.57-1.51)	.66	
Sex					
Male	38/1456	59/1448	0.61 (0.40-0.93)	.02	.79
Female	26/433	40/440	0.62 (0.36-1.06)	.08	
BMI					
<28	62/1684	91/1674	0.68 (0.49-0.94)	.02	.26
≥28	2/205	8/214	0.38 (0.05-2.71)	.26	
Diabetes					
Yes	13/418	23/398	0.51 (0.24-1.08)	.06	.75
No	51/1471	76/1490	0.72 (0.50-1.04)	.07	
Hypertension					
Yes	38/948	54/959	0.73 (0.48-1.10)	.12	.35
No	26/941	45/929	0.58 (0.35-0.95)	.03	
Dyslipidemia					
Yes	7/454	15/452	0.57 (0.22-1.49)	.25	.33
No	57/1435	84/1436	0.70 (0.50-0.98)	.03	
Current smoking					
Yes	20/828	27/790	0.70 (0.40-1.22)	.20	.98
No	44/1061	72/1098	0.64 (0.44-0.94)	.02	
Previous PCI					
Yes	2/96	5/105	0.43 (0.08-2.18)	.10	.67
No	62/1793	94/1783	0.66 (0.48-0.91)	.01	
Hospital level					
Provincial	4/233	13/248	0.34 (0.12-0.98)	.04	.76
Prefecture/county	60/1656	86/1640	0.69 (0.49-0.96)	.03	
Onset-to-arrival time, h					
<6	42/1485	67/1473	0.64 (0.43-0.94)	.02	.78
6-12	15/277	23/276	0.52 (0.23-1.19)	.12	
>12	7/127	9/139	0.68 (0.21-2.24)	.51	
Anterior myocardial infarction					
Yes	38/905	63/913	0.59 (0.39-0.89)	.01	.63
No	26/984	36/975	0.68 (0.40-1.14)	.12	
Killip class at admission					
I and II	52/1848	86/1843	0.60 (0.42-0.84)	<.01	.19
III and IV	12/41	13/45	0.82 (0.24-2.87)	.61	
Infarct-related artery					
LAD	33/803	45/770	0.67 (0.42-1.06)	.10	.48
Non-LAD	21/919	24/896	0.79 (0.43-1.43)	.41	
Reperfusion therapy					
Yes	51/1656	71/1629	0.71 (0.49-1.02)	.06	.38
No	13/233	28/259	0.45 (0.22-0.89)	.02	
Thrombolysis	4/95	14/123	0.32 (0.10-1.08)	.05	.29
PPCI	47/1560	57/1504	0.80 (0.54-1.19)	.28	
Statins					
Yes	50/1824	67/1811	0.72 (0.50-1.04)	.09	.13
No	14/65	32/77	0.79 (0.41-1.53)	.55	
Nitrates					
Yes	45/1441	65/1431	0.69 (0.47-1.01)	.05	.56
No	19/448	34/457	0.67 (0.37-1.18)	.13	
β-Blockers					
Yes	27/1205	46/1201	0.56 (0.34-0.93)	.02	.60
No	37/684	53/687	0.80 (0.51-1.19)	.23	
ARBs/ACEIs/ARNI					
Yes	15/962	24/989	0.77 (0.40-1.48)	.42	.92
No	49/927	75/899	0.62 (0.43-0.90)	.01	
Diuretics (excluding spironolactone)					
Yes	26/523	47/532	0.54 (0.33-0.87)	.01	.39
No	38/1366	52/1356	0.73 (0.48-1.02)	.15	
Spironolactone					
Yes	17/418	24/416	0.70 (0.38-1.29)	.26	.75
No	47/1471	75/1472	0.66 (0.45-0.95)	.02	



Killip classes are defined in footnote c of Table 1. P2Y12 receptor inhibitors, aspirin, statins, nitrates, β-blockers, angiotensin II receptor blockers (ARBs)/angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor–neprilysin inhibitor (ARNI), diuretics, and spironolactone refer to medication during hospitalization.

Because of the small numbers and/or wide CIs, prespecified subgroup analyses were not presented according to previous heart failure, previous myocardial infarction, receiving aspirin, or P2Y12 receptor inhibitors. The benefit of Tongxinluo was similar across all these prespecified subgroups.

Figure 3. Kaplan-Meier Curves for 1-Year Major Adverse Cardiac and Cerebrovascular Events (MACCEs) and Individual Components of MACCEs



HR indicates hazard ratio.

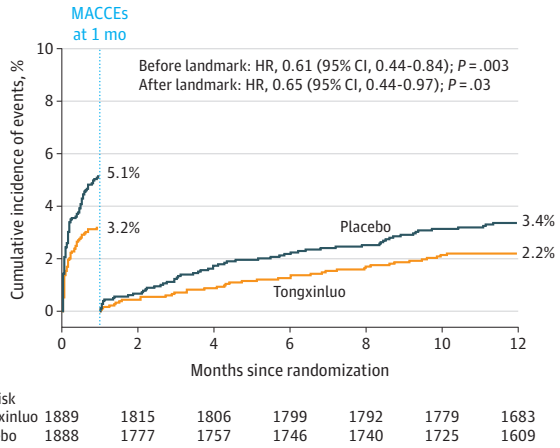
numbers were even lower at discharge (Table 2, 57.0% for β-blockers and 49.6% for ACEIs/ARBs; and eTable 2 in Supplement 3), suggesting potential underuse of guideline-directed medical therapy. Reperfusion therapy was performed in 87.0% of patients, among which 81.1% were primary PCI and 5.8% were thrombolysis. Elective PCI was performed on 10.9% of patients before discharge. The median length of hospital stay was 9 days (IQR, 8-12).

Primary and Secondary Outcomes

In the primary analysis population, the primary end point occurred in 64 patients (3.4%) in the Tongxinluo group vs 99 patients (5.2%) in the placebo group (RR, 0.64 [95% CI, 0.47 to 0.88]; RD, −1.8% [95% CI, −3.2% to −0.6%]) (**Table 3**). Individual components of the primary end point, including 30-day cardiac death (56 [3.0%] vs 80 [4.2%]; RR, 0.70 [95% CI, 0.50 to 0.99]; RD, −1.2% [95% CI, −2.5% to −0.1%]) and myocardial reinfarction (0 [0%] vs 9 [0.5%]; RR, 0.35 [95% CI, 0.13 to 0.99]; RD, −0.5% [95% CI, −0.8% to −0.2%]) were significantly lower in the Tongxinluo group. There was no statistically significant difference in the 30-day stroke rate. There was no emergent coronary revascularization within 30 days in both groups. The benefit of Tongxinluo in 30-day MACCEs was similar across all prespecified and exploratory subgroups (**Figure 2**; eFigure in Supplement 3). Similar results were also found in the intention-to-treat and per-protocol analyses (eTables 3 and 4 in Supplement 3), and further confirmed in the sensitivity analyses of imputation of missing 30-day MACCE values (eTable 5 in Supplement 3). Additionally, 30-day severe STEMI complications also favored Tongxinluo (221 [11.8%] vs 277 [14.8%]; RR, 0.80 [95% CI, 0.68 to 0.94]; RD, −3.0% [95% CI, −5.2% to −0.8%]) (Table 3).

As compared with the placebo group, the Tongxinluo group also had a lower 1-year MACCE rate (100 [5.3%] vs 157 [8.3%]; HR, 0.64 [95% CI, 0.49 to 0.82]; RD, −3.0% [95% CI, −4.6% to −1.4%]) (Table 3 and **Figure 3**), with a significant reduction as well after the 30-day landmark point (HR, 0.65 [95% CI, 0.44 to 0.97]; **Figure 4**). Risks were also decreased for the majority of individual components of MACCEs, including 1-year cardiac death (85 [4.5%] vs 116 [6.1%]; HR, 0.73 [95% CI, 0.55 to 0.97]; RD, −1.6% [95% CI, −3.1% to −0.2%]), myocardial reinfarction (6 [0.3%] vs 21 [1.1%]; HR, 0.26 [95% CI, 0.10 to 0.67]; RD, −0.8% [95% CI, −1.3% to −0.3%]), and stroke (10 [0.5%] vs 24 [1.3%]; HR, 0.44 [95% CI, 0.21 to 0.92]; RD, −0.8%

Figure 4. Post Hoc Landmark Analysis at 30-Day Point for 1-Year Major Adverse Cardiac and Cerebrovascular Events (MACCEs)



MACCEs are a composite of cardiac death, myocardial reinfarction, emergent coronary revascularization, and stroke. HR indicates hazard ratio.

[95% CI, −1.3% to −0.1%]) (Table 3 and Figure 3). There were no statistically significant differences in major bleeding at 30 days (8 [0.4%] vs 13 [0.7%]; RR, 0.58 [95% CI, 0.24 to 1.43]; RD, −0.3% [95% CI, −0.8% to 0.2%]) and 1 year (13 [0.7%] vs 19 [1.0%]; HR, 0.66 [95% CI, 0.32 to 1.35]; RD, −0.3% [95% CI, −0.9% to 0.3%]). In addition, Tongxinluo reduced 1-year rehospitalization due to heart failure (16 [0.9%] vs 35 [1.9%]; HR, 0.48 [95% CI, 0.26 to 0.87]; RD, −1.0% [95% CI, −1.7% to −0.3%]). There was no statistically significant difference in 1-year all-cause mortality (97 [5.1%] vs 124 [6.6%]; HR, 0.77 [95% CI, 0.59 to 1.01]; RD, −1.5% [95% CI, −2.9% to 0.1%]). The rates of stent thrombosis were not significantly different between the groups.

Among 3285 patients (87.0%) who received reperfusion therapy, the mean (SD) ST-segment resolution of the lead with maximal ST-segment elevation was more prominent in the Tongxinluo group (−0.26 [0.19] mV) than that in the placebo group (−0.24 [0.19] mV) at 24-hour reperfusion (mean difference, −0.02 mV [95% CI, −0.03 to −0.01 mV]; P = .01) (Table 3). There were no statistically significant differences in ST-segment resolution at 2 hours and 7 days and myocardial no reflow as defined as ST-segment resolution of 50% or less at 2 hours or 75% or less at 24 hours or 7 days.

Adverse Events

Nonfatal serious adverse events occurred in 41 patients (2.2%) in the Tongxinluo group and 52 (2.8%) in the placebo group (P = .25). Compared with the placebo group, the Tongxinluo group had more adverse drug reactions (40 [2.1%] vs 21 [1.1%]; P = .02), mainly driven by symptoms in the digestive system such as stomach discomfort and nausea. The adverse drug reactions that required treatment occurred in 9 patients (0.5%) in the Tongxinluo group and 8 patients (0.4%) in the placebo group, respectively (P > .99). Specific adverse events are listed in eTable 6 in Supplement 3.

Discussion

In this randomized clinical trial of Chinese patients with STEMI, Tongxinluo as an adjunctive therapy in addition to guideline-directed treatments reduced the primary end point of 30-day MACCEs, as well as secondary outcomes of cardiac death, myocardial reinfarction, and severe STEMI complications at 30 days. These clinical benefits persisted at 1-year follow-up, with no significant difference in major bleeding and adverse events. Further research is needed to determine the mechanism of action of Tongxinluo in STEMI.

Tongxinluo, which means "to open (tong) the network (luo) of the heart (xin)," was approved for angina pectoris and ischemic stroke in China in 1996.[4] Although its safety and efficacy were not fully evaluated prior to its approval, a number of preclinical studies and a small mechanistic trial have been conducted. Tongxinluo has been shown to promote myocardial microvascular perfusion and reduce myocardial ischemic/reperfusion injury through the protection of endotheliocytes and cardiomyocytes from ischemic/reperfusion-induced death.[10-18,25] Furthermore, Tongxinluo may also stabilize coronary vulnerable plaques and retard their progression by mitigating intraplaque inflammation and neovascularization.[26] Further evidence was also provided by the Carotid Artery Plaque Intervention With Tongxinluo Capsule (CAPITAL) Trial, showing that Tongxinluo could stabilize artery plaques, reduce major cardiovascular events, and delay the time to first event.[27] The current study was the first large, randomized, double-blind, placebo-controlled, multicenter clinical trial to evaluate the efficacy and safety of Tongxinluo as an adjunctive treatment of guideline-directed therapies (including primary PCI) in community-based Chinese patients with STEMI and found Tongxinluo improved both 30-day and 1-year clinical outcomes.

Traditional Chinese medicine, with its unique theory and practice, is often questioned for no basis in modern science, lack of identified active component, and no objective and/or quantitative evaluation criteria for its safety and efficacy.[28] As of today, there are only a few clinical trials that have evaluated the clinical benefit of traditional Chinese medicine.[28] Yet these trials are often limited due to small sample sizes, use of surrogate end points, unclear blinding methods, and diverse outcomes reported.[19,28] Unlike most traditional Chinese medicine research with relatively low level of evidence, the current study design incorporated all key elements of randomized clinical trials, including randomization, placebo control, blinding, prespecified outcome measures and SAP, and blinded clinical end point committee adjudication. In addition, the database and analyses were independently validated by a third-party analytical center. Therefore, the current study may serve as a model for future clinical trials to evaluate the safety and efficacy of traditional Chinese medicine.

Limitations

This study has some limitations. First, the Tongxinluo capsule is a traditional Chinese medicine compound of multiple plant and insect products. Despite the clinical benefit

demonstrated in this trial, the active ingredient(s) and the exact mechanism of action remain to be established. Second, physicians were instructed to provide guideline-recommended medical therapy. However, β-blockers were prescribed to 64% of the patients and ACEIs or ARBs were prescribed to 51% to 52% of patients during hospitalization. The utilization rates were even lower at discharge. The suboptimal use of guideline-directed medical therapy, which is expected to reduce mortality, could affect the magnitude of the benefit of Tongxinluo. Third, likely due to the COVID-19 pandemic and physicians' concern over the efficacy and safety of Tongxinluo, more than 90% of patients were presenting with Killip class I, which may have explained the lower rates of MACCEs and STEMI complications. While this limitation is partially overcome by the subgroup analysis showing consistent results across Killip class, the efficacy of Tongxinluo in patients with higher-risk profiles needs to be evaluated further. Fourth, patient adherence with the therapy (maintenance dose of 4 capsules, 3 times a day) may be lower outside the clinical trial setting. Fifth, because the patients in this trial were all Chinese, the generalizability needs to be further evaluated in other populations, especially in countries with better adherence to guideline-directed medical therapy.

Conclusions

Among patients with STEMI, the Chinese patent medicine Tongxinluo, as an adjunctive therapy in addition to STEMI guideline-directed treatments, significantly improved both 30-day and 1-year clinical outcomes. Further research is needed to determine the mechanism of action of Tongxinluo in STEMI.

ARTICLE INFORMATION

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Author Affiliations: State Key Laboratory of Cardiovascular Disease, Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (Yuejin Yang, X. Li, Chen, H. Zhang, Y. Wu, J. Zhang, J. Li, An, Guan, L. Li, Gao); Departments of Neurology and Population and Data Science, University of Texas Southwestern Medical Center, Dallas (Xian); Emergency Center, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (Yanmin Yang); Department of Cardiology, Xiuyan Manchu Autonomous County Central People's Hospital, Anshan, Liaoning, China (J. Wu); Department of Cardiology, Xihua County People's Hospital, Zhoukou, Henan, China (C. Wang); Department of Cardiology, Northern Jiangsu People's Hospital, Yangzhou, Jiangsu, China (He); Department of Cardiology, The First Affiliated Hospital of the Medical College, Shihezi University, Shihezi, Xinjiang, China (Zhong Wang); Department of Cardiology, Xiajin People's Hospital of Shandong Province, Xiajin, Shandong, China (Y. Wang); Department of Cardiology, Xinxiang Central Hospital, Xinxiang, Henan, China (Zhifang Wang); Department of Cardiology, Anyang District Hospital, Anyang, Henan, China (Liu); Department of Cardiology, Shihezi People's Hospital, Shihezi, Xinjiang, China (X. Wang); Department of Cardiology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China (M. Zhang); Department of Biostatistics, Peking University Clinical Research Institute, Peking University First Hospital, Beijing, China (Shang, Yao); Department of Cardiology, General Hospital of Northern Theater Command, Shenyang, Liaoning, China (Han); State Key Laboratory of Component-Based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China (B. Zhang); Department of Medicine, University of Texas Southwestern Medical Center, Dallas (Peterson).

Author Contributions: Dr Yuejin Yang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Yuejin Yang, X. Li, Chen, and Xian contributed equally to this article.
Concept and design: Yuejin Yang, Xian, Yao, Peterson.
Acquisition, analysis, or interpretation of data: Yuejin Yang, X. Li, Chen, H. Zhang, Y. Wu, Yanmin Yang, J. Wu, C. Wang, He, Zhong Wang, Y. Wang, Zhifang Wang, Liu, X. Wang, M. Zhang, J. Zhang, J. Li, An, Guan, L. Li, Shang, Yao, Han, B. Zhang, Gao, Peterson.
Drafting of the manuscript: Yuejin Yang, Chen.
Critical review of the manuscript for important intellectual content: X. Li, Chen, Xian, H. Zhang, Y. Wu, Yanmin Yang, J. Wu, C. Wang, He, Zhong Wang, Y. Wang, Zhifang Wang, Liu, X. Wang, M. Zhang, J. Zhang, J. Li, An, Guan, L. Li, Shang, Yao, Han, B. Zhang, Gao, Peterson.
Statistical analysis: Shang, Yao.
Obtained funding: Yuejin Yang.
Administrative, technical, or material support: Yuejin Yang, X. Li, Chen, H. Zhang, Y. Wu, Yanmin Yang, J. Wu, C. Wang, He, Zhong Wang, Y. Wang, Zhifang Wang, Liu, X. Wang, M. Zhang, J. Zhang, J. Li, An, Guan, L. Li, Gao, Peterson.
Supervision: Yuejin Yang, C. Wang, Gao.

Conflict of Interest Disclosures: Dr Yuejin Yang reported receiving grants from Shijiazhuang Yiling Pharmacological Co Ltd and the National Key Research and Development Program of China during the conduct of the study; in addition, Dr Yuejin Yang had a patent related to the mechanisms of Tongxinluo in alleviating rat myocardial reperfusion injury (license No. ZL 2019 1 0535074.8) and a patent related to the mechanisms of Tongxinluo on enhancing the protective effects of exosomes derived from mesenchymal stem cells in rat acute myocardial infarction (license No. ZL 2021 1 0738185.6). Dr Chen reported having a patent related to the mechanisms of Tongxinluo in alleviating rat myocardial reperfusion injury (license No. ZL 2019 1 0535074.8). Dr Peterson reported receiving grants from Amgen and Esperion Therapeutics and personal fees from Janssen and Novo Nordisk during the conduct of the study. No other disclosures were reported.

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Group Information: A complete list of the CTS-AMI trial investigators and study center appears in Supplement 4.

Disclaimer: Dr Peterson is an Editorial Board member of *JAMA*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Meeting Presentation: This study was presented at the American Heart Association meeting; November 6, 2022; Chicago, Illinois.

Data Sharing Statement: See Supplement 5.

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REFERENCES

1. Heusch G. Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nat Rev Cardiol*. 2020;17(12):773-789. doi:10.1038/s41569-020-0403-y

2. Figtree GA, Vernon ST, Hadziosmanovic N, et al. Mortality in STEMI patients without standard modifiable risk factors: a sex-disaggregated analysis of SWEDEHEART registry data. *Lancet*. 2021;397(10279):1085-1094. doi:10.1016/S0140-6736(21)00272-5

3. Hillerson D, Li S, Misumida N, et al. Characteristics, process metrics, and outcomes among patients with ST-elevation myocardial infarction in rural vs urban areas in the US: a report from the US National Cardiovascular Data Registry. *JAMA Cardiol*. 2022;7(10):1016-1024. doi:10.1001/jamacardio.2022.2774

4. Karalliedde LD, Kappagoda CT. The challenge of traditional Chinese medicines for allopathic practitioners. *Am J Physiol Heart Circ Physiol*. 2009;297(6):H1967-H1969. doi:10.1152/ajpheart.00944.2009

5. Chen WQ, Zhong L, Zhang L, et al. Chinese medicine Tongxinluo significantly lowers serum lipid levels and stabilizes vulnerable plaques in a rabbit model. *J Ethnopharmacol*. 2009;124(1):103-110. doi:10.1016/j.jep.2009.04.009

6. Ma H, Hao J, Liu H, et al. Peoniflorin preconditioning protects against myocardial ischemia/reperfusion injury through inhibiting myocardial apoptosis: RISK pathway involved. *Appl Biochem Biotechnol*. 2022;194(3):1149-1165. doi:10.1007/s12010-021-03680-z

7. Yuan C, Wang H, Yuan Z. Ginsenoside Rg1 inhibits myocardial ischaemia and reperfusion injury *via* HIF-1 α-ERK signalling pathways in a diabetic rat model. *Pharmazie*. 2019;74(3):157-162. doi:10.1691/ph.2019.8858

8. Li L, Pan CS, Yan L, et al. Ginsenoside Rg1 ameliorates rat myocardial ischemia-reperfusion injury by modulating energy metabolism pathways. *Front Physiol*. 2018;9:78. doi:10.3389/fphys.2018.00078

9. Li CY, Yang P, Jiang YL, et al. Ginsenoside Rb1 attenuates cardiomyocyte apoptosis induced by myocardial ischemia reperfusion injury through mTOR signal pathway. *Biomed Pharmacother*. 2020;125:109913. doi:10.1016/j.biopha.2020.109913

10. Cui H, Li X, Li N, et al. Induction of autophagy by Tongxinluo through the MEK/ERK pathway protects human cardiac microvascular endothelial cells from hypoxia/reoxygenation injury. *J Cardiovasc Pharmacol*. 2014;64(2):180-190. doi:10.1097/FJC.0000000000000104

11. Chen GH, Xu CS, Zhang J, et al. Inhibition of miR-128-3p by Tongxinluo protects human cardiomyocytes from ischemia/reperfusion injury via upregulation of p70s6k1/p-p70s6k1. *Front Pharmacol*. 2017;8:775. doi:10.3389/fphar.2017.00775

12. Chen G, Xu C, Gillette TG, et al. Cardiomyocyte-derived small extracellular vesicles can signal eNOS activation in cardiac microvascular endothelial cells to protect against ischemia/reperfusion injury. *Theranostics*. 2020;10(25):11754-11774. doi:10.7150/thno.43163

13. Li Q, Li N, Cui HH, et al. Tongxinluo exerts protective effects via anti-apoptotic and pro-autophagic mechanisms by activating AMPK pathway in infarcted rat hearts. *Exp Physiol*. 2017;102(4):422-435. doi:10.1113/EP086192

14. Yang YJ, Zhao JL, Jing ZC, et al. Beneficial effects of Tong-xin-luo (herb) on myocardial no-reflow after acute myocardial infarction and reperfusion: experiment of mini-swine model. In Chinese. *Zhonghua Yi Xue Za Zhi*. 2005;85(13):883-888.

15. Cheng YT, Yang YJ, Zhang HT, et al. Pretreatment with Tongxinluo protects porcine myocardium from ischaemia/reperfusion injury through a nitric oxide related mechanism. *Chin Med J (Engl)*. 2009;122(13):1529-1538.

16. Li XD, Yang YJ, Geng YJ, et al. Tongxinluo reduces myocardial no-reflow and ischemia-reperfusion injury by stimulating the phosphorylation of eNOS via the PKA pathway. *Am J Physiol Heart Circ Physiol*. 2010;299(4):H1255-H1261. doi:10.1152/ajpheart.00459.2010

17. Li XD, Yang YJ, Cheng YT, Dou KF, Tian Y, Meng XM. Protein kinase A-mediated cardioprotection of Tongxinluo relates to the inhibition of myocardial inflammation, apoptosis, and edema in reperfused swine hearts. *Chin Med J (Engl)*. 2013;126(8):1469-1479.

18. Zhang HT, Jia ZH, Zhang J, et al. No-reflow protection and long-term efficacy for acute myocardial infarction with Tongxinluo: a randomized double-blind placebo-controlled multicenter clinical trial (ENLEAT Trial). *Chin Med J (Engl)*. 2010;123(20):2858-2864.

19. Xu Y, Li X, Zhang H, et al. China Tongxinluo Study for myocardial protection in patients with acute myocardial infarction (CTS-AMI): rationale and design of a randomized, double-blind, placebo-controlled, multicenter clinical trial. *Am Heart J*. 2020;227:47-55. doi:10.1016/j.ahj.2020.06.011

20. Ibanez B, James S, Agewall S, et al; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177. doi:10.1093/eurheartj/ehx393

21. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2016;133(11):1135-1147. doi:10.1161/CIR.0000000000000336

22. Shah A, Feldman DN. Outcome of the HORIZONS-AMI trial: bivalirudin enhances long-term survival in patients with ST-elevation myocardial infarction undergoing angioplasty. *Vasc Health Risk Manag*. 2012;8:115-123. doi:10.2147/VHRM.S23491

23. Xu H, Wiviott SD, Sabatine MS, et al. Outcomes and readmission rate within 30 days and 6 months after acute myocardial infarction in China: data from the China Acute Myocardial Infarction Registry. *J Am Coll Cardiol*. 2016;67(13)(suppl):506. doi:10.1016/S0735-1097(16)30507-1

24. Abraha I, Montedori A. Modified intention to treat reporting in randomised controlled trials: systematic review. *BMJ*. 2010;340:c2697. doi:10.1136/bmj.c2697

25. Qi K, Li X, Geng Y, et al. Tongxinluo attenuates reperfusion injury in diabetic hearts by angiopoietin-like 4-mediated protection of endothelial barrier integrity via PPAR-α pathway. *PLoS One*. 2018;13(6):e0198403. doi:10.1371/journal.pone.0198403

26. Zhang L, Liu Y, Lu XT, et al. Traditional Chinese medication Tongxinluo dose-dependently enhances stability of vulnerable plaques: a comparison with a high-dose simvastatin therapy. *Am J Physiol Heart Circ Physiol*. 2009;297(6):H2004-H2014. doi:10.1152/ajpheart.00208.2009

27. Zhang M, Liu Y, Xu M, et al. Carotid Artery Plaque Intervention With Tongxinluo Capsule (CAPITAL): a multicenter randomized double-blind parallel-group placebo-controlled study. *Sci Rep*. 2019;9(1):4545. doi:10.1038/s41598-019-41118-z

28. Hao P, Jiang F, Cheng J, Ma L, Zhang Y, Zhao Y. Traditional Chinese medicine for cardiovascular disease: evidence and potential mechanisms. *J Am Coll Cardiol*. 2017;69(24):2952-2966. doi:10.1016/j.jacc.2017.04.041