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# ORIGINAL ARTICLE

## Effect of Danlou Tablet (丹蒌片) on Peri-procedural Myocardial Injury among Patients undergoing Percutaneous Coronary Intervention for Non-ST Elevation Acute Coronary Syndrome: A Study Protocol of A Multicenter, Randomized, Controlled Trial*

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**ABSTRACT** **Background:** It has been shown that administration of statins reduced the risk of peri-procedural myocardial damage. However, it remains unclear whether Chinese medicine Danlou Tablet (丹蒌片), similar to statins, may protect patients undergoing percutaneous coronary intervention (PCI) from peri-procedural myocardial damage. **Objective:** To demonstrate the hypothesis whether treatment with Danlou Tablet would improve clinical outcome in patients undergoing selective PCI with non-ST elevation acute coronary syndrome (NSTE-ACS) in China. **Methods:** Approximately 220 patients with unstable angina or non-ST-segment elevation myocardial infarction undergoing PCI will be enrolled and randomized to Danlou Tablet treatment (4.5 g/day for 2 days before intervention, with a further 4.5 g/day for 90 days thereafter) or placebo. All patients will not receive Danlou Tablet before procedure. The primary end point is to evaluate the incidence of cardiac death, myocardial infarction or unplanned re-hospitalization and revascularization after 30 days in patients undergoing selective PCI treated with Danlou Tablet compared with placebo. Secondary endpoints include the incidence of peri-procedural myocardial injury, 3-month clinical outcomes, the quality of life and Chinese medicine syndromes assessment. **Conclusion:** This study protocol will provide important evidence of Danlou Tablet treatment on the peri-procedural myocardial injury in patients with NSTE-ACS undergoing selective PCI, which may support a strategy of routine Danlou Tablet therapy to improve the clinical outcomes.

**KEYWORDS** non-ST-segment elevation acute coronary syndrome, percutaneous coronary intervention, Danlou Tablet, peri-procedural myocardial infarction, Chinese medicine

Over the past few years, a high incidence of adverse cardiovascular events following percutaneous coronary intervention (PCI), including peri-procedural myocardial injury, received a great deal of attention in spite of major improvements in this therapy.[1] As estimated, 75,000 to 450,000 patients with coronary artery disease have sustained a peri-procedural myocardial injury, in which the incidence is similar to the annual rate of spontaneous myocardial infarction. Peri-procedural myocardial injury, also known as myocardial necrosis was assessed by cardiac biomarker elevation. As many retrospective observational studies found that the extent of cardiac biomarkers increase is related to subsequently adverse cardiovascular events and mortality rate.[2] Despite many strategies have been proposed to address this issue, procedural ischemic myocardial injury remains the primary complication after coronary angioplasty.[3]

Recently, many clinical trials demonstrated the efficacy of 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) in significant reduction of peri-procedural myocardial infarction in patients with acute coronary syndromes following coronary intervention.[4] For instance, the ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) trial revealed that treatment with atorvastatin in statin-naive patients undergoing selective PCI for chronic stable angina was associated with a considerable decrease in the occurrence of peri-procedural myocardial



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injury.[5] This myocardial protection was confirmed by the ARMYDA-ACS (Atorvastatin for Reduction of Myocardial Damage During Angioplasty–Acute Coronary Syndromes) trial, in which a pre-treatment with high-dose atorvastatin 12-h prior to procedure of coronary revascularization in statin-naive patients with acute coronary syndromes undergoing early invasive strategy improved outcomes during a period of 30-day follow-up.[6] Furthermore, the ROMA (Rosuvastatin Pretreatment in Patients Undergoing Elective PCI to Reduce the Incidence of Myocardial Periprocedural Necrosis) trial established that a single, high loading dose of rosuvastatin (40 mg) within 24 h before elective PCI in patients with stable coronary artery disease could decrease the rate of post-procedural elevation of cardiac biomarkers compared with the standard treatment.[7] Nevertheless, high-dose or even super-high-dose statin pretreatment and maintenance might increase the risk of liver damage or rhabdomyolysis.[8] Therefore, numerous studies, including that presented in this paper, aim at elucidating whether such myocardial injury could be averted after administration of some natural herbs or agent that reduce the incidence of peri-procedural myocardial necrosis after non-emergency coronary angioplasty.[3]

Chinese medicine (CM) has been practiced for thousands of years and a series of studies have suggested that it bring multiple benefits to people with coronary heart disease (CHD) due to the discovery of their effectiveness in alleviating symptoms of myocardial infarction, angina pectoris, arrhythmia, hypertension and other cardiovascular conditions.[9] In particular, Danlou Tablet (丹蒌片), a Chinese patent medicine, has been successfully utilized by many cardiologists and internists for its induction of promoting blood circulation and eliminating phlegm. It consists of the following ingredients: *Salvia*, *miltiorrhiza* Bunge, *Ligusticum chuanxiong* Hort, *Trichosanthes kirilowii* Maxim and *Allium macrostemon* Bunge, etc.

Moreover, recent experimental research has indicated that Danlou Tablet may reduce blood lipid level of rats with hyperlipidemia and improve vascular endothelial function in rats with arterial endothelial injury.[10] In addition, it could reduce myocardial necrosis area and promote infarct healing, prevention and treatment of early left ventricular remodeling in rats exposed to myocardial ischemia-reperfusion injury.[11] Importantly, a multicenter trial demonstrated that administration of Danlou Tablet improved clinical symptoms, inhibited the inflammation reaction of patients with CHD and decreased the frequency of major atherogenetic complications (plaque rupture and thrombosis).[12] Thus, we hypothesized that administration of Danlou Tablet may provide benefits for myocardial necrosis in patients with acute coronary syndrome (ACS) undergoing invasive surgery, which is similar to statins.

## METHODS

### Aim of the Study

The primary objective is to evaluate the major adverse cardiac clinical events (MACE) in terms of cardiac death, peri-procedural myocardial infarction (MI), spontaneous MI and target vessel revascularization (TVR). According to the literature, the peri-procedural MI was defined as a creatine kinase-MB (CK-MB) elevation >3 upper limit of normal (ULN) value alone or associated with chest pain in patients undergoing PCI.

The secondary objective is to evaluate the efficacy of the sequential peri-PCI Danlou Tablet treatment strategy, which means pre-PCI loading doses of Danlou Tablet and post-PCI Danlou Tablet treatment for 30 days, in reducing 30-day primary cardiovascular endpoints in patients undergoing PCI with non-ST elevation acute coronary syndrome, and the rate of peri-procedural rise of myocardial biomarkers (troponin I and CK-MB and hyper sensitive C-reactive protein (hs-CRP) greater than the normal value within 8 and 24 h after PCI. In addition, the effect of Danlou Tablet treatment on the serum level of triglycerides and cholesterol, and the efficacy of peri-procedural CM therapy on clinical outcomes including quality of life and CM syndromes 3 months following surgery will also be investigated.

### Study Design

This is a multicenter, randomized, prospective, double-blind, placebo-controlled, parallel-group study performed in 9 institutions (Guangdong Provincial Hospital of Chinese Medicine; Xiyuan Hospital of China Academy of Chinese Medical Sciences; Yueyang Hospital of Integrated Medicine of Shanghai University of Chinese Medicine; Dongfang Hospital of Beijing University of Chinese Medicine; First Affiliated Hospital of Zhejiang University of Chinese Medicine; China-Japan Friendship Hospital of Ministry of Health; Affiliated Hospital of Guangdong Medical College; First Affiliated Hospital of Henan College of Chinese Medicine; Tianjin

Chest Hospital; Wuyi Hospital of Chinese Medicine of Jiangmen City). This study has been reviewed and approved by the Institutional Ethics Committee at Guangdong Provincial Hospital of Chinese Medicine (B2011-41-01) and is currently enrolled in the Chinese Clinical Trail Registry (ChiCTR-TRC-12001929). All patients have to personally sign and date an informed consent document before randomization.

### Study Population

The inclusion criteria included: patients' age greater than 18 and less that 80 years old, selective coronary angiography due to non-ST-segment elevation ACS, unstable angina or non-ST elevation (NSTE) acute myocardial infarction. Eligible patients also suffer from the Chinese medicine syndrome of intermingled phlegm and blood stasis (IPBS) based on its own theory.

According to the protocol, clinical exclusion criteria included ST-segment elevation acute myocardial infarction (STEMI); NSTE-ACS with a high risk for emergency coronary angiography; previous myocardial infarction within 30 days, cardiac shock or left ventricular ejection fraction <30%; a history of taking any dose of statin (such as simvastatin, pravastatin, fluvastatin or rosuvastatin) during the past 2 weeks; hepatic dysfunction, active hepatic disease, or elevated of alanine aminotransferase and aspartate aminotransferase serum levels; severe renal dysfunction (serum creatinine concentration> 3 mg/dL or 264 μmol/L); myopathy or elevated creatine kinase; serious adverse reaction to Danlou Tablet or statins; malignant disease or other diseases with life expectancy <6 months; participate in other interventional clinical trials using drugs or devices; pregnancy or lactation; the increased risk of adverse event or abnormal laboratory finding.

### Interventions and Comparisons

Enrolled patients will be randomly allocated to indicated study group according to a computer-generated site-stratified, block randomization schedule. Eligible patients were randomized to receive placebo or Danlou Tablet (4.5 g/day for 2 consecutive days before coronary angiography, with a further 4.5 g/day for 90 days after the procedure). Simultaneously, all patients after intervention were received standard ischemic and antihypertensive therapy according to patients' conditions, such as aspirin, clopidogrel, angiotensin-converting enzyme inhibitors or β-blockers, irrespective of the initial randomization assignment. Physicians will prescribe these medicines according to the clinical guidelines. In particular, atorvastatin was unified administrated so that patients from both groups do not receive any dose of statins before the coronary angiography whereas receive atorvastatin 10 mg/day for 90 days after the procedure. Three-month clinical follow-up was scheduled in all study patients by investigators at 30 days and 3 months after the procedure. Physicians performing the procedure and the follow-up assessment were not aware of the randomization assignment.

Blood samples were collected and baseline standard biomarkers, including CK-MB and troponin I, were determined at admission time. Following the procedure, levels of CK-MB and troponin-I were assessed at 8-, 12-, and 24-h post-PCI. Levels of C-reactive protein (CRP) were also measured before PCI and at 8, 12 and 24 h after intervention. The ULN was defined as the 99th percentile of normal population with a total imprecision of 10%, according to Joint European Society of Cardiology/American College of Cardiology guidelines. CK-MB and troponin-I values were considered abnormal if >3 ULN (0.01 ng/mL). Pre-procedural and post-procedural electrocardiograms were performed. Peri-procedural values of total and low-density lipoprotein (LDL) cholesterol were measured.

### End Points

The primary end point of this trial was 30-day incidence of MACE: cardiac death, MI, documented unstable angina requiring revascularization (bypass surgery or repeat PCI), rehospitalization due to severe angina and heart failure for a 30-day period after randomization.

Peri-procedural myocardial infarction was defined as a post-procedural increase of CK-MB >5 ULN, which is consistent with the consensus statement of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction for clinical trials on coronary intervention.

Secondary end points of the study were: (1) any post-procedural changes of myocardial biomarkers (CK-MB and troponin-I) occurring within 24 h of the procedure; (2) post-procedural variations from baseline of CRP levels at 8 and 24 h after the procedure; (3) serum levels of triglycerides and cholesterol before treatment and 90 days after PCI;

and (4) quality of life by Seattle Angina Scale and CM syndromes scale during 3-month follow-up; (5) proportion of patients who take a reduced dose of atorvastatin, withdraw from the study treatment, or withdraw from the study due to adverse events over 3-month follow-up. Study design is shown in Figure 1.

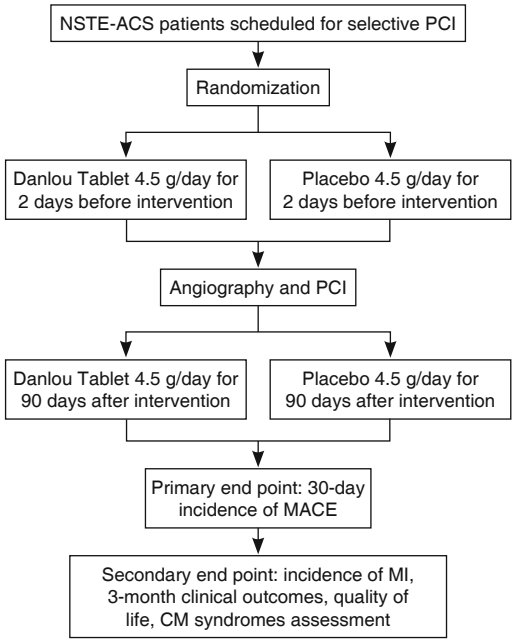


**Figure 1. Study Design of Danlou Tablet for Patients with ACS undergoing PCI**

Notes: CK-MB: creatine kinase-MB; hs-CRP: high sensitive C-reactive protein; MI: myocardial infarction; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; TVR: target vessel revascularization

### Sample Size Estimation

The objective of the statistical test on the primary response is to detect a difference in the incidence of primary endpoint events between the experiment and the control groups within 30 days after PCI. In the ARMYDA-ACS trial,[6] the morbidity of MACEs in the control group without intervention of statin was around 17%. With the protocol presented in this study, it is expected that MACEs in the experiment and the control groups will be 5% and 17%, respectively. On the basis of a two-sided test size of a level of 5% and a power of 80%, it has been calculated that a minimum of 99 patients would be required for each group (total 198 patients). Allowing for 10% of patients who may withdraw from the study within 3 months after PCI, 232 eligible cases will be required.

## DISCUSSION

Some impressive trials showed clinical benefit of treatment with statins in patients undergoing PCI for ACS, such as ARMYDA (Atorvastatin for Reduction of MYocardial Damage During Angioplasty, 81% risk reduction of periprocedural myocardial infarction), MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; 16% risk reduction),[13] A to Z (Aggrastat to Zocor; 25% risk reduction), ARMYDA-ACS (88% risk reduction) or PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy; 28% risk reduction).

However, the possible mechanisms underlying these cardio-protective effects of statin are indistinguishable. Because of a longer duration of medication, this could not be attributable to cholesterol-lowering effects.[14] Experimental evidence indicates various lipid-independent and pleiotropic effects of statin treatment for instance improvement of endothelial function,[15] vasodilation of coronary microvessels,[16] and direct antithrombotic effect. Furthermore, experimental studies have demonstrated that Chinese herbs, in particular Danlou Table, have cardio-protective effects, similar to statin, in the animal model of hyperlipidemia, arterial endothelial injury and acute ischemia.[10-11,17] Despite these advances, the incidence of side-effect in treatment with statins, like rhabdomyolysis or liver damage, should not be ignored. Therefore, this study protocol has been designed to assess whether Danlou Tablet may improve clinical outcomes in patients with ACS (unstable angina or non-ST-segment elevation myocardial infarction) undergoing PCI.

Inflammation, reflected by the level of hs-CRP, contributes to the pathogenesis of coronary artery disease.[18] Myocardial necrosis is associated with an increase in inflammatory biomarkers.[19] Elevation of both pre-procedural and/or post-procedural hs-CRP is an independent predictor of a higher incidence of MACE.[20] The anti-inflammatory effects of Danlou Tablet are demonstrated in a previous clinical study,[12] suggesting that Danlou Tablet may play an important role in improving outcomes in patients with hs-CRP. Thus the assessment of hs-CRP in the current study protocol is necessary.

Furthermore, the unified statin management included in the current study protocol, i.e., neither groups receive any dose of statin before PCI and receive a usual dose of statin post PCI, was enforced in order to eliminate the confounding factor coming from statin pretreatment on the background of complying with the ethical principles. The results of this study will

provide important evidence on the efficacy and safety of peri-procedural serial CM pre-treatment in patients with ACS syndrome undergoing selective PCI. Besides the 30-day primary outcomes, this study is going to evaluate the incidence of 3-month MACEs and find out whether short-term Danlou Tablet therapy could yield long-term benefit for patients undergoing PCI.

## Conflict of Interest

None of authors received funding or research grants from the relevant drug manufacturers in this research. The authors declare that they have no conflict of interests.

## Author Contributions

Wang L, Mao S, Qi JY, Yi Ren, Chen KJ, and Zhang MZ were involved in study design and writing the manuscript. Guo XF contributed to study conducting and data analysis. All authors read and approved the final manuscript.

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