

# Efficacy of INTensive Treatment Versus Standard Treatment of COMpound DanshEn Dripping Pills in Refractory Angina Patients With Incomplete Revascularization (INCODER Study): Study Protocol for a Multicenter, Double-blind, Randomized Controlled, Superiority Trial

**Zexuan Wu**

Department of Cardiology, the First Affiliated Hospital, sun yat-sen university

**Danping Xu**

Cardiac disease treatment center, Guangdong Provincial Hospital of Traditional Chinese Medicine

**Zhen Wu**

Department of Cardiology, the Third affiliated hospital of Sun yat-sen University

**Ailan Chen**

Department of Cardiology, the first affiliated hospital of Guangzhou medical university

**Lin Xu**

Department of Cardiology, General Hospital of Guangzhou Military Command of PLA: People's Liberation Army General Hospital of Southern Theatre Command

**Yuling Zhang**

Department of Cardiology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University

**Li Ling**

Department of Medical Statistics, School of Public Health, Sun Yat-sen University

**Yan Zhou**

Department of Cardiology, Hainan General Hospital

**Yin Liu**

Department of Cancer Epidemiology, Henan Cancer Hospital, Affiliated cancer hospital of Zhengzhou University

**Yugang Dong**

Department of Cardiology, the first affiliated hospital, Sun Yat-sen University

**Yili Chen** (✉ [chenyil7@mail.sysu.edu.cn](mailto:chenyil7@mail.sysu.edu.cn))

Department of Cardiology, the first affiliated hospital, Sun yat-sen University <https://orcid.org/0000-0001-8455-9378>

## Research Article

**Keywords:** compound danshen dripping pills, intensive treatment, efficacy, refractory angina, incomplete revascularization

**Posted Date:** April 16th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-306596/v1>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Introduction:** Patients with incomplete revascularization (ICR) tend to develop refractory angina despite optimal medical therapy. Compound Danshen Dripping Pills (CDDP) is a widely used antianginal drug in China and is showed to significantly alleviate myocardial ischemia. Previous studies showed dose-efficacy tendency when increasing doses of CDDP. The study is aim to investigate the efficacy and safety of intensive doses of CDDP in patients with refractory angina with ICR.

**Methods and Analysis:** The INCODER study is a multicenter, double-blind, randomized controlled, superiority trial. We plan to recruit 250 patients aged 18 to 85 years with a diagnosis of refractory angina with ICR. Patients will be randomized (1:1) to intensive treatment group (CDDP 20 pills three times per day) or control group (10 pills CDDP and 10 pills placebo three times per day). Patients will have a 6-week medication period and be followed up every two weeks. The primary end point is the change of total exercise time from baseline to week 6 as assessed by cardiopulmonary exercise testing (CPET). Secondary end points include changes in frequency of angina, Canadian Cardiovascular Society angina class, nitroglycerin use, Seattle Angina Questionnaire scores, O<sub>2</sub> uptake kinetics and other parameters as measured by CPET, and levels of plasma C-reactive protein, homocysteine and N-terminal pro-B-type natriuretic peptide. Safety events related to CDDP use will be monitored.

**Ethics and dissemination:** The research had been approved by the Clinical research and laboratory animal ethics committee of the First Affiliated Hospital, Sun Yat-sen University ([2019]65). The results will be reported through peer-reviewed journals, seminars and conference presentations.

**Trial registration number:** [www.chictr.org.cn](http://www.chictr.org.cn) (ChiCTR2000032384). Registered on 27 April 2020.

## Background

Multivessel coronary artery disease (CAD), which is defined as a stenosis of > 50% affecting more than one epicardial vessel, is found in about 50% of patients on diagnostic angiography and is significantly associated with worse prognosis than single-vessel CAD.<sup>1,2</sup> Due to various reasons including older age, multiple comorbidities (particularly diabetes mellitus) and complex coronary lesions such as chronic total occlusions, bifurcation disease, diffuse disease or narrow segments, as well as multiple lesions, about 43.3% of patients underwent percutaneous coronary intervention (PCI) and 36.8% underwent coronary artery bypass grafting (CABG) cannot achieve complete revascularization (CR).<sup>2,3</sup> According to the New York's PCI registry that included 41 639 New York residents with multivessel coronary artery disease undergoing PCI, the rate of ICR was up to 78% among patients with ST-segment elevation myocardial infarction and 71% among other patients.<sup>4</sup> These patients were associated with recurrent cardiovascular events, frequent hospital re-admissions and decreased quality of life.<sup>5,6</sup> Despite optimal medical therapy (OMT), up to 10–15% of CAD patients develop refractory angina with an annual mortality rates as high as 4%.<sup>7–9</sup> Complete revascularization may be a choice for patients who are in good condition, however, recent studies have shown controversial results on the prognosis benefit of PCI over OMT in stable

patients<sup>10,11</sup>. Therefore, there is an unmet need for additional medical strategies to alleviate anginal symptoms and improve prognosis for patients with ICR. The ESC guidelines recommend using ranolazine, ivabradine, nicorandil or trimetazidine as a second-line therapy for patients with persistent angina according to heart rate, blood pressure, and tolerance (class IIa, level of evidence B).<sup>9</sup> However, the RIVER-PCI study showed no incremental benefits in improving angina symptoms, quality of life or prognosis for patients with ICR by adding ranolazine.<sup>12,13</sup> Evidence were also lacking on the efficacy of ivabradine, trimetazidine or nicorandil in patients with ICR.<sup>14</sup> Consequently, robust randomized, controlled trials aiming on more effective pharmacological agents for these challenging population are in urgent need.

Compound Danshen Dripping Pills (CDDP) or Dantonic, an herbal patent medicine, is widely used in China for clinical treatment of CAD. CDDP contains three medicinal herbs, salvia miltiorrhiza, notoginseng, and borneol at a ratio of 450:141:8 (g).<sup>15</sup> Its main active pharmacodynamic substances are phenolic acids, saponins and borneol.<sup>16</sup> According to previous studies, CDDP played an important role in the management of CAD through regulating multiple targets that were associated with thrombosis, hyperlipidemia, and vascular remodeling etc.<sup>17</sup> A meta-analysis comprising of 60 randomized controlled clinical trials, including a total of 6 931 patients, showed that CDDP is apparently more effective than isosorbide dinitrate in the treatment of angina pectoris.<sup>18</sup> Another systematic review analysis including 34 071 patients with coronary heart disease (including patients with angina pectoris and acute myocardial infarction) confirmed the benefits of CDDP in patients with coronary heart disease.<sup>19</sup> The recommended doses for CAD is 10 pills, three times per day in China.<sup>16</sup> In the Phase II clinical trial of CDDP conducted under the supervisions of FDA in the US, a total of 125 patients with moderate chronic stable angina pectoris were randomly divided into three groups: placebo, low or high dose group (0, 20 pills, or 30 pills, twice per day). And the results showed a significant dose-response relationship regarding total exercise duration (TED) following the standard Bruce protocol. After 4 weeks of treatment, the mean improvement of TED compared to placebo was 20 s in low dose group (P = 0.18) and 43 s in high dose group (P = 0.005). No serious adverse drug reactions (ADRs) were observed.<sup>16</sup> Although the changes of TED between low and high dose group were not significantly different, a tendency was observed in better improvement of TED in higher dose treatment. For patients with refractory angina with ICR, we found a dose-efficacy tendency when increasing doses to 20 pills three times per day in clinical practice. Considering more serious conditions, no options or refusal for revascularization, poor response to traditional medical treatment, as well as different races and nationalities compared with FDA phase II clinical trial, we designed this study and inferred intensive doses of CDDP would be better in improvement of exercise capacity in patients with refractory angina without CR.

As for the safety issue, according to the reports from China FDA (CFDA) center for ADRs, the incidence rate of ADRs for CDDP is only 0.0018%, most of which were gastrointestinal symptoms, nonspecific hemorrhage, nonspecific purpura, etc.<sup>16</sup> Most of the ADR were mild and reversible.

Therefore, we design the study to evaluate the efficacy and safety of Intensive treatment versus standard treatment of Compound Danshen dripping pills in Refractory angina patients with ICR (INCODER study).

## Methods And Analysis

### Study design

The INCODER study is a multicenter, randomized, double-blind, parallel controlled, superiority clinical trial. Patients will be randomly divided into two groups: intensive treatment group (CDDP 20 pills three times per day) or control group (CDDP 10 pills three times per day). Figure 1 shows the design and procedures through the trial.

### Study hypothesis

The administration of CDDP 20 pills three times per day is superior to 10 pills three times per day with respect to efficacy and safety in patients with refractory angina with ICR.

### Study population, eligibility criteria and recruitment

Patients aged 18 to 85 years with a diagnosis of stable refractory angina with ICR are eligible for participation. Patients were eligible for inclusion in the study if they had a history of CAD with refractory angina (Canadian Cardiovascular Society [CCS] class II to III) despite optimal medical therapy for at least one month. Optimal medical therapy is defined as guideline-recommended treatment including secondary prevention and at least two antianginal drugs: one is nitrates, another is beta-blocker or calcium channel blocker, except for medication contraindications.<sup>20</sup> ICR is defined as the presence of  $\geq 1$  lesion with visually estimated  $\geq 50\%$  diameter stenosis in any coronary artery (including branch vessels) of  $\geq 2.0$  mm in diameter, whether in the target vessel or in a nontarget vessel. In the case of a participant post-CABG, ICR is defined as the presence of  $\geq 1$  lesion with visually estimated  $\geq 50\%$  diameter stenosis in a nonbypassed epicardial vessel  $\geq 2.0$  mm in diameter, or  $\geq 1$  visually estimated  $\geq 50\%$  diameter stenosis in a bypass graft supplying an otherwise nonrevascularized myocardial territory.<sup>21</sup> The ejection fraction should be at least 30%. Patients are willing to sign the informed consent form.

The exclusion criteria are detailed in Table 1. Patients with acute coronary syndrome within 1 month or planned coronary revascularization during the study period, or history of transient ischemia attack within 2 months are excluded. Patients with severe joint diseases, severe peripheral vascular disease, severe pulmonary hypertension, uncontrolled chronic obstructive pulmonary disease and other comorbidities that might affect the results of the cardiopulmonary exercise testing are excluded. We also exclude patients with abnormalities in electrocardiogram in the rest including preexcitation syndrome ventricular pacing rhythm, ST segment depressed more than 1 mm in the rest, left bundle branch block or any intraventricular conduction block and QRS duration more than 120 ms that might influence the interpretation of the termination of CPET. Patients with severe comorbidity, pregnant or lactation are also excluded. Study candidates will be assessed for eligibility within 2 weeks prior to enrolment.

Table 1  
Eligibility criteria

**Inclusion criteria**

1. Age 18 to 85 years.
2. Had a history of coronary artery disease with refractory angina [Canadian Cardiovascular Society (CCS) class II to III] despite optimal medical therapy for at least one month.
  - Optimal medical therapy is defined as guideline-recommended treatment including secondary prevention and at least two antianginal drugs: one is nitrates, another is beta-blocker or calcium channel blocker, except for medication contraindications.
3. With incomplete revascularization (ICR).
  - ICR is defined as the presence of  $\geq 1$  lesion with visually estimated  $\geq 50\%$  diameter stenosis in any coronary artery (including branch vessels) of  $\geq 2.0$  mm in diameter, whether in the target vessel or in a nontarget vessel. In the case of a participant post-CABG, ICR is defined as the presence of  $\geq 1$  lesion with visually estimated  $\geq 50\%$  diameter stenosis in a nonbypassed epicardial vessel  $\geq 2.0$  mm in diameter, or  $\geq 1$  visually estimated  $\geq 50\%$  diameter stenosis in a bypass graft supplying an otherwise nonrevascularized myocardial territory.
4. The ejection fraction  $\geq 30\%$ .<sup>a</sup>
5. Willing to sign the informed consent form.

**Exclusion criteria**

1. Acute coronary syndrome within 1 month or planned coronary revascularization during the study period;
2. Episode of transient ischemia attack, ischemic or hemorrhagic stroke within 2 months;
3. Presence of neuromuscular, orthopedic or other non-cardiac condition such as severe peripheral artery disease, severe pulmonary hypertension and uncontrolled chronic obstructive pulmonary disease or asthma that prevents the patient from exercise testing on a cycle ergometer;
4. Patients with the following resting electrocardiographic abnormalities that might influence the interpretation of the termination of CPET:
  - Pre-excitation (Wolff-Parkinson-White) syndrome
  - Electronically paced ventricular rhythm
  - 1 mm or more of resting ST depression
  - Complete left bundle-branch block or any interventricular conduction defect with a QRS duration greater than 120 ms
5. Uncontrolled symptomatic heart failure;
6. Moderate to severe symptomatic aortic stenosis;

7. Hypertrophic cardiomyopathy;
8. Acute myocarditis or pericarditis;
9. Active endocarditis;
10. Acute pulmonary embolism;
11. Suspected or known acute aortic dissection;
12. Severe hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg at screening);
13. Severe anemia (Hemoglobin < 60 g/L);
14. Active psychosis requiring anticonvulsant treatment;
15. Pregnant or lactating women.
16. Participation in other clinical studies within 30 days before the first visit.

CABG, coronary artery bypass grafting; CPET, cardiopulmonary exercise testing.

<sup>a</sup> Echocardiographic results measured with 3 months before obtaining informed consent can be used for assessing eligibility.

The study will be conducted in 10 medical centers in China. Patients will be recruited by local physicians using posters and advertisement in the hospital and nearby communities. Posters and advertisements contain brief introductions about the study and the contact information of the investigators. The study will be detailed explained to the potential participants and informed written consent will be obtained prior to enrolment.

## Randomization, allocation and blinding

Randomization is generated using computer-generated random permuted blocks by a designated statistician not involved in study operations using SAS V9.4 software. Either CDDP or placebo will be packaged identically and labeled with a number according to the randomization list. The treatment kit numbers will be obtained by the investigators at the time of patients' randomization and treatment kits will be strictly sequentially allocated to patients according to the randomization list. In accordance with the double-blind design, the sponsor, study patients, investigators and study site personnel will remain blinded to study treatment.

The randomization code will be kept in opaque sealed envelopes and secured by both the sponsor and the principal investigator and can only be broken in exceptional circumstances when knowledge of the investigational drug is essential for treating the patient. If the randomization code is uncovered, the investigator should document the reason for unblinding, and the administration of investigational drug will be discontinued.

## Intervention

The intensive treatment group is administered with CDDP (produced by Tasly Pharmaceutical Group Co. Ltd., China) at a dose of 20 pills three times per day while the control group taking a traditional dose of 10 pills CDDP and 10 pills placebo three times per day orally after meals. All the patients will be treated for 6 weeks. CDDP or placebo pills are identical in size and smell. Every 20 pills (20 pills CDDP for intensive treatment group or 10 pills CDDP and 10 pills placebo for control group) are stored in one identical bottle. Patients take one bottle three times per day.

## **Concomitant medication**

Study participants should be treated with standard CAD therapies as per recommended guidelines. The following drugs are prohibited during the whole study including ivabradine, ranolazine, nicorandil, trimetazidine and other antianginal Chinese traditional medicine (including ginkgo biloba dropping pill, ginkgolide dropping pill, Shexiang Baoxin Pill, Xinkeshu tablet, Naoxintong, Naoxingqing, xueshuantong, Di'ao xinxuekang capsule, Yinzhan xinmai dropping pill, Xinnaoxin, Zhenyuan capsule, Suxiao Jiuxin Pill, Tongxinluo, Guanxin Danshen Dropping Pill, yindanxintai dropping pill, etc). However, other kinds of medications are taken as needed. The concomitant medication will be recorded throughout the trial and analyzed if necessary.

## **Outcomes**

### **Primary outcome**

The primary outcome is the change in total exercise time evaluated by CPET from baseline to week 6 in the intention-to-treat (ITT) population.

### **Secondary outcomes**

The secondary outcomes include change from baseline to week 6 in the following parameters including frequency of angina, nitroglycerin use, CCS angina class improvement, Seattle Angina Questionnaire (SAQ) scores, CPET indexes as well as plasma C-reactive protein (CRP), homocysteine and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Safety assessment includes adverse events during the whole study period, vital signs, physical examination, 12-lead electrocardiogram (ECG), laboratory tests and rescue medication use (Table 2).

Table 2  
Efficacy and safety endpoints

**Primary endpoint**

The changes in total exercise time evaluated by CPET from baseline to week 6

**Secondary endpoint**

The changes of the following parameters from baseline to week 6

1. Frequency of angina
2. Frequency of nitroglycerine use
3. Proportion of patients experiencing an improvement of  $\geq 1$  CCS angina classes
4. Proportion of patients experiencing an improvement of  $\geq 2$  CCS angina classes
5. The SAQ scores subdivided in the following 5 dimensions
  - Physical limitation;
  - Anginal stability;
  - Anginal frequency;
  - Treatment satisfaction;
  - Disease perception.
6. CPET parameters
  - Peak  $VO_2$  (ml/min)
  - Peak  $VO_2$  (ml/min/kg)
  - $VO_2$  at anaerobic threshold (ml/min)
  - $VO_2$  at anaerobic threshold (ml/min/kg)
  - Peak METs
  - Peak work rate (W)
  - $O_2$  pulse at peak exercise (mL/beat)
  - $P_{ET}O_2$  at peak exercise (mmHg)
  - $P_{ET}CO_2$  at peak exercise (mmHg)

- VE/VCO<sub>2</sub> slope

-  $\Delta\text{VO}_2/\Delta\text{work-rate}$  (ml/min/W)

7. Plasma CRP, homocysteine and NT-proBNP

### **Safety endpoints**

1. Treatment-emergent adverse event

2. Vital signs

3. Physical examination

4. ECG

5. Clinical laboratory tests

CPET: cardiopulmonary exercise testing; CCS, Canadian Cardiovascular Society; SAQ, Seattle Angina Questionnaire; VO<sub>2</sub>, Oxygen uptake; METs, metabolic equivalent levels; P<sub>ET</sub>O<sub>2</sub>, partial pressure of end-tidal oxygen; P<sub>ET</sub>CO<sub>2</sub>, partial pressure of end-tidal carbon dioxide; VE/VCO<sub>2</sub>, Ventilatory equivalent of carbon dioxide; CRP, C-reactive protein; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; ECG: electrocardiography.

## **Study Timelines**

### **Screening visit (Week – 2)**

Schedule of enrolment and assessments are listed in Table 3. Subjects will be evaluated at the screening visit 2 weeks prior to enrolment through a complete medical history, vital signs, physical examination, 12-lead ECG, transthoracic echocardiography (TTE), eligibility laboratory tests and a review of concomitant medications. Eligibility and baseline laboratory examinations include urine pregnancy testing for women with childbearing potential, complete blood count, serum lipids, biochemical tests, coagulation test and cardiac biomarkers. Baseline parameters for efficacy evaluation including CRP, homocysteine and NT-proBNP will also be examined. TTE measured with 3 months before obtaining informed consent can be used for eligibility assessment. Severity of angina will be assessed including CCS angina class, frequency of angina attack and nitroglycerin use.

Table 3  
Schedule of assessments

Visit number	V1	V2	V3	V4	V5
Week	-2	0	2	4	6
Day	-14 ± 3	0	14 ± 3	28 ± 3	42 ± 3
Informed consent	x				
Inclusion/ exclusion criteria	x	x			
Medical history	x	x			
Concomitant medication	x	x	x	x	x
Vital signs	x	x	x	x	x
Physical examination	x	x	x	x	x
urine pregnancy testing <sup>a</sup>	x				
12-lead ECG	x	x	x	x	x
Transthoracic echocardiography <sup>b</sup>	x				
CCS class	x	x	x	x	x
SAQ scores		x	x	x	x
Frequency of angina	x	x	x	x	x
CPET		x			x
Laboratory tests <sup>c</sup>	x				x
Dispense study medication and collect empty study medication		x	x	x	x
Dispense nitroglycerin and collect the remaining pills;	x	x	x	x	x
Compliance evaluation		x	x	x	x
Adverse events	x	x	x	x	x
ECG: electrocardiogram; CCS, Canadian Cardiovascular Society; SAQ: Seattle angina questionnaire; CPET: cardiopulmonary exercise testing.					
<sup>a</sup> Urine pregnancy testing for women with childbearing potential for eligibility.					
<sup>b</sup> Echocardiographic results measured with 3 months before obtaining informed consent can be used for assessing eligibility.					
<sup>c</sup> Laboratory tests for efficacy and safety include:					

Visit number	V1	V2	V3	V4	V5
- Complete blood count					
- Serum lipids					
- Biochemical indexes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK) and creatinine					
- Coagulation indexes: prothrombin time (PT), partially activated prothrombin time (APTT), international normalized ratio (INR), coagulation time (TT), fibrinogen (FBG) and D-dimer					
- Cardiac biomarkers: myoglobin (MYO), cardiac troponin T (cTnT) and creatine kinase-MB isoenzyme (CK-MB)					
- Parameters for efficacy: C-reactive protein (CRP), homocysteine and amino-terminal pro-B-type natriuretic peptide (NT-proBNP).					

## Wash-out period

Patients who are taking other antianginal drugs that are contraindicated in our study at screening will be asked to start a 2-week wash-out period, in which they will discontinue the antianginal drugs and follow the optimal medical therapy. Nitroglycerin is allowed during the wash-out period and should be recorded when used.

## Baseline visit (Week 0)

Research participants will complete all baseline procedures, including: clinical evaluation, angina assessment, SAQ scores and CPET. Patients who fulfill all the inclusion criteria and none of the exclusion criteria will be randomized with a 1:1 allocation ratio to receive either CDDP 20 pills three times per day or 10 pills three times per day. Nitroglycerin will also be dispensed for angina attack when needed. Patients are asked to record every angina attack and nitroglycerin consumption during the study.

## Follow-up visit (Week 2 and week 4)

Patients will be followed up every two weeks to assess safety and tolerability. Vital signs, physical examination, angina assessment and SAQ scores will be recorded. Any adverse events during the intervening period since screening/ baseline visit will be recorded. Study drug dispensed at screening/ baseline visit will be collected for compliance calculation.

## Final evaluation (Week 6)

Final evaluations will be conducted 6-weeks following the baseline assessment. Vital signs, physical examination, 12-lead ECG, angina assessment, SAQ scores, laboratory analyses and adverse events will be assessed. Blood analyses including CRP, homocysteine and NT-proBNP for efficacy assessments and other parameters for safety assessments consistent with baseline will be performed. CPET will be conducted for efficacy evaluation.

# Data collection, management, and analysis

## Sample collection and laboratory measurements

Blood sample collection is scheduled at screening/randomization and at the final visit. Blood samples are first collected into evacuated tubes, clot for 30 min at room temperature, and then centrifugated for 10 min at  $3000 \times g$  at room temperature. Beckman Coulter AU5800 chemistry analyzer are used for further measurements. Urine samples will also be collected at screening for urine pregnancy test for women with childbearing potential. All the laboratory measurements mentioned above will be performed at the Department of Laboratory Medicine of each site with consistent external quality control.

## Angina Assessment

CCS angina class, SAQ scores, frequency of angina attack and nitroglycerin use will be recorded for angina assessment during the whole study period. The SAQ scores measure five important dimensions of CAD including physical limitation, anginal stability, anginal frequency, treatment satisfaction and disease perception.<sup>22</sup>

## Cardiopulmonary Exercise Testing

CPET is conducted on an electronically braked cycle ergometer (Ergoline GmbH, Germany) using a ramp protocol according to the statement from the American Heart Association.<sup>23,24</sup> Expired gases are collected and analyzed breath by breath. The test includes several stages<sup>23</sup>: 1) rest for 3 minutes: measurements of rest ECG, blood pressure, heart rate and pulse oxygen saturation. 2) unloading exercise for 3 minutes; 3) incremental exercise: The increment rate is set between  $10 \text{ W}\cdot\text{min}^{-1}$  to  $20 \text{ W}\cdot\text{min}^{-1}$  based on patients' characteristics in order to obtain approximately 10 min duration. The resistance gradually increases every six seconds. All patients are instructed to cycle with a pedal frequency of 60 revolutions per minute (rpm), and are encouraged to keep exercising until exhaustion, or symptoms of chest tightness, chest pain and shortness of breath, or inability to maintain the pedal frequency of 60 rpm. 4) recovery: unloading exercise for 3 minutes, then rest 5 to 10 minutes. The blood pressure is measured by using Tango M2 Stress Test Monitor. The heart rate is determined from the electrocardiogram and expressed as the percentage of the predicted value ( $220 - \text{age}$ ). The 12-lead electrocardiogram is continuously recorded during the test. Symptoms were assessed by means of the Borg's Rating of Perceived Exertion (RPE, Borg's 6–20 Scale).<sup>25</sup> Peak exercise was considered the highest  $\text{VO}_2$  achieved during active exercise or early recovery. Heart rate and respiratory exchange ratio (RER) are objective indicators for peak exercise. Peak  $\text{VO}_2$  was determined as the highest mean  $\text{VO}_2$  over 20 s.<sup>24</sup> Parameters measured during CPET in our study are listed in supplementary Table 1. The indications of termination of the test are detailed in supplementary Table 2. The total exercise time and reason for termination will be recorded.

## Compliance evaluation

Compliance will be evaluated by counting the number of bottles returned at every follow-up visit (total doses taken divided by total prescribed doses). Of note, the denominator (total prescribed doses) will be calculated over the actual duration the subject is in the study. Subjects will be informed of the intention to monitor compliance in the informed consent form.

## **Adverse events and safety**

Adverse events will be assessed and recorded in the case report forms during the whole study. Given the nature of the intervention, the most common adverse reactions related to CDDP including gastrointestinal symptoms, headache and facial flushing will be monitored. Although CPET is fairly safe with the serious complications rate of < 1 to 5 per 10 000 tests and death rate around 0.5 per 10 000 tests, complications do occur and should be paid attention.<sup>24,26</sup> Major complications include death, myocardial infarction, angina pectoris, arrhythmia, hemodynamic instability and orthopedic injury.<sup>21</sup> Therefore, the test should strictly follow the guideline for exercise stress testing especially the indications to stop the test (Supplementary Table 2).

All serious adverse events (SAEs) will be assessed and reported to the ethics committee in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (GCP) guidelines.<sup>27</sup>

## **Data management and monitoring**

Data will be collected by trained research staff at each site and recorded in case report forms. This will then be entered into the INCODER database, which is located in clinical research unit in department of cardiology in the First Affiliated Hospital, Sun Yat-sen University and supervised by the trial data manager. Data from the INCODER study will be transferred securely to the Research Data Deposit at <http://www.researchdata.org.cn/>, where it can be accessed and traced securely via a specialized administration panel by members of the research team using an encrypted password.

The INCODER study will be overseen by the trial steering committee (TSC) in accordance with the GCP guidance. The TSC, which consists of the chief investigator, study coordinator, site investigators and statisticians, will independently monitors the process the study and give advice on the continuation, termination or amendments of the trial protocol. The study is sponsored by Tasly Pharmaceutical Group Co. Ltd. and will be subject to regular monitoring visits and audits.

## **Patient and public involvement**

Patients were not involved in the design or in the recruitment to and conduct of the study, nor in the assessment of burden of the intervention. Results will be disseminated to participants on request.

## **STATISTICAL CONSIDERATION**

### **Sample size assumptions**

This is a superiority study. Sample size calculation is based on the primary outcome of change in total exercise time from baseline to follow-up at 6 weeks. According to the unpublished results of Phase II clinical trial conducted in the USA<sup>16</sup> and our preliminary study (<http://www.chictr.org.cn>; Registration number: ChiCTR-IIR-17013662), the change of total exercise time is  $62.5 \pm 19.6$  s and  $54.5 \pm 18.8$  s from baseline to week 6 in intensive treatment group and control group respectively. We therefore assumed the changes of total exercise time as 62.5 s and 54.5 s in the two groups and both standard deviations as 20%. A sample size of 100 per group will yield 80% power to obtain a significant difference between the 2 groups, using a 2-sample t test at a 1-sided 0.025 level of significance. Considering an approximately 20% dropout rate, a total of 250 subjects (125 subjects for each group) will be enrolled.

## Statistical analysis

Statistical analysis will be conducted by the SAS V9.4 software, using a two-tailed 0.05 significance level.

Baseline demographic characteristics of two groups will be presented using descriptive statistics: Continuous variables will be presented with median and interquartile range or mean  $\pm$  SD. Categorical variables will be expressed as frequencies and percentages. For comparisons between two groups, t test or rank sum test will be used for continuous variables, the chi-square or Fisher's exact test will be applied for categorical variables.

The primary outcome, changes of total exercise time between the intensive treatment group and the control group, will be estimated based on the ITT population consisting of all the randomized patients. General linear model will be used for the primary outcome with covariates of center and baseline exercise time using a 1-sided 0.025 significance level. Data will be presented as mean differences and corresponding *p* values. Missing data will be imputed by using the last observation carried forward method.

We will further conduct ITT and per-protocol analysis to evaluate the differences in certain secondary outcomes between the two groups. Safety analyses will also be conducted based on a safety set in which all randomized subjects receiving  $\geq 1$  dose of study medication.

## ETHICS AND DISSEMINATION

The protocol was approved by the Clinical Research and Laboratory Animal Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University ([2019]65) and all participants will provide their written informed consent. All study procedures are followed with the ethical standards of the Helsinki Declaration. The study protocol was registered at [www.chictr.org.cn](http://www.chictr.org.cn) (ChiCTR2000032384) prior to trial commencement.

Changes to the study protocol are documented in amendments. Amendments are submitted for approval to the Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University. Major changes will be updated on the trial registration website of [www.chictr.org.cn](http://www.chictr.org.cn).

After completion, the results will be published in a peer-reviewed journal.

## Discussion

Over the past decades, there are great advances in interventional therapy and medical therapy in CAD. However, still a large proportion of patients cannot achieve CR and are complaining of refractory angina.<sup>6,25,26</sup> Some of these patients refuse coronary revascularization due to poor economic condition, while a majority of patients for whom traditional revascularization is not an option. These patients may be old age with excessive comorbidities, including chronic renal insufficiency or bleeding diathesis, or have multiple coronary lesions, or even absent vascular access.<sup>28</sup> Even for the patients have the opportunities for revascularization, recent studies found no evidence that an initial invasive strategy, as compared with an initial conservative medical therapy, reduced the risk of ischemic cardiovascular events or all-cause mortality.<sup>10,11</sup> Although mortality in this patient population has decreased, enhancing quality of life remains a challenge. Considering the growing “no option” patients who are inadequately responsive to “conventional” medical management and the limitations of invasive intervention, novel pharmacologic therapeutic strategies aiming at the improvement of angina symptoms, quality of life and overall cardiac prognosis are of important clinical significance.

CDDP is a traditional Chinese herb patent medicine and has been demonstrated to be effective in CAD patients. In the FDA Phase II clinical trial conducted in US, there was a dose-response tendency in the mean improvement of total exercise duration in high dose group and low dose group when compared with placebo.<sup>16</sup> In clinical practice, we also found that intensive treatment of CDDP was better than traditional dose regarding refractory angina patients with ICR. However, robust randomized clinical trials are in great need. To be noted, the study population in our study are those without complete revascularization and still complaining of angina, which usually have more commodities and are much worse than those in the FDA Phase II clinical trial in US. Moreover, considering the differences in races and patients' conditions, we infer that intensive dose of CDDP may bring extra benefits. To evaluate the feasibility of our study, we conducted a preliminary study aiming at the refractory angina patients who were unsuitable for revascularization (<http://www.chictr.org.cn>; Registration number: ChiCTR-IIR-17013662). However, due to the difficulties in the patients' recruitment and enrollment, we expanded the scope of the inclusive patients to those with ICR. During the preliminary study, we also found it very important to unify the criteria for termination of the CPET test. Therefore, we optimized the termination criteria (Supplementary Table 2.) and quality control of the test, making sure that the termination was symptom or ischemia limited, but not patient subjective to stop.

Of note, the gold standard to evaluate the exercise tolerance is treadmill exercise testing.<sup>29</sup> However, for the treadmill exercise testing, the patients are passively moving and may not keep up with the speed of the treadmill or may be fear of falling down. As for the CPET, patients are encouraged to exercise to the limit and patients are allowed to stop by themselves when emergency. Therefore, our study adopts a relatively safe test of CPET to evaluate the exercise capacity of the high-risk patients. Furthermore, CPET

enables us to collect more fitness and metabolic parameters including peak VO<sub>2</sub>, METs and work load, from which we can have a better understanding of patients' cardiopulmonary function and exercise tolerance. Our study may provide high quality clinical evidence for the management of refractory angina patients without CR.

## **Trial Status**

Patient recruitment was started in August 2020 according to the protocol of version 4.0, 05-Nov-2019. Up to Mar 2021, a total of 17 patients had been enrolled. The study is expected to conclude in December 2022.

## **Declarations**

### **Ethics approval and consent to participate**

The research and the protocol have been approved by the Clinical Research and Laboratory Animal Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University ([2019]65). Written, informed consent to participate will be obtained from all study participants.

### **Availability of data and materials**

Not applicable. Study patient enrollment and data collection is currently ongoing and no datasets were generated for analysis yet.

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

The INCODER study is sponsored by Tasly Pharmaceutical Group Co. Ltd (Grant number: K0601461). The study design, data collection, statistical analysis, or publications are not influenced by the sponsors and are exclusive responsibility of the investigators.

### **Author's contributions**

All the authors contributed to the design and development of the study protocol, and have reviewed the manuscript. Yugang Dong and Yili Chen conceived and instructed the study. Zexuan Wu, Danping Xu and Zhen Wu designed the study. Li Ling and Yin Liu provided statistical expertise and supported the development of the statistical analysis plan. Ailan Chen, Lin Xu, Yuling Zhang and Yan Zhou contributed to recruitment, trial oversight, intervention implementation as well as the follow up of the subjects.

### **Acknowledgements**

None.

## References

1. Emond M, Mock MB, Davis KB, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. 1994;90(6):2645-57.
2. Sandoval Y, Brilakis ES, Canoniero M, et al. Complete versus incomplete coronary revascularization of patients with multivessel coronary artery disease. *Curr Treat Options Cardiovasc Med*. 2015;17(3):366.
3. Head SJ, Mack MJ, Holmes DR, et al. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg*. 2012;41(3):535-41.
4. Hannan EL, Zhong Y, Berger PB, et al. Association of Coronary Vessel Characteristics With Outcome in Patients With Percutaneous Coronary Interventions With Incomplete Revascularization. *JAMA Cardiol*. 2018;3(2):123-30.
5. Cordero A, Lopez-Palop R, Carrillo P, et al. Addition of Antiangina Drugs and Recurrent Cardiovascular Events Associated With Incomplete Revascularization in Acute Coronary Syndrome. *Rev Esp Cardiol (Engl Ed)*. 2018;71(3):217-19.
6. Task Force M, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949-3003.
7. Henry TD, Satran D, Hodges JS, et al. Long-term survival in patients with refractory angina. *Eur Heart J*. 2013;34(34):2683-8.
8. Henry TD, Satran D, Jolicoeur EM. Treatment of refractory angina in patients not suitable for revascularization. *Nat Rev Cardiol*. 2014;11(2):78-95.
9. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. *Eur Heart J*. 2002;23(5):355-70.
10. Maron DJ, Hochman JS, Reynolds HR, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med*. 2020;382(15):1395-407.
11. Bangalore S, Maron DJ, O'Brien SM, et al. Management of Coronary Disease in Patients with Advanced Kidney Disease. *N Engl J Med*. 2020;382(17):1608-18.
12. Alexander KP, Weisz G, Prather K, et al. Effects of Ranolazine on Angina and Quality of Life After Percutaneous Coronary Intervention With Incomplete Revascularization: Results From the Ranolazine for Incomplete Vessel Revascularization (RIVER-PCI) Trial. *Circulation*. 2016;133(1):39-47.
13. Weisz G, Genereux P, Iniguez A, et al. Ranolazine in patients with incomplete revascularisation after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial. 2016;387(10014):136-45.

14. Ferrari R, Ford I, Fox K, Marzilli M, et al. A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of Trimetazidine in patients with angina pectoris having been treated by percutaneous coronary intervention (ATPCI study): Rationale, design, and baseline characteristics. *Am Heart J.* 2019;210:98-107.
15. Commission CP. Pharmacopoeia of the People's Republic of China. *China Medical Science Press.* 2015;1:292-93.
16. Writing Group of Recommendations of Expert Panel from Chinese Geriatrics Society on the Clinical Use of Compound Danshen Dripping P. Recommendations on the Clinical Use of Compound Danshen Dripping Pills. *Chin Med J (Engl).* 2017;130(8):972-78.
17. Li X, Xu X, Wang J, et al. A system-level investigation into the mechanisms of Chinese Traditional Medicine: Compound Danshen Formula for cardiovascular disease treatment. *PLoS One.* 2012;7(9):e43918.
18. Jia Y, Huang F, Zhang S, et al. Is danshen (*Salvia miltiorrhiza*) dripping pill more effective than isosorbide dinitrate in treating angina pectoris? A systematic review of randomized controlled trials. *Int J Cardiol.* 2012;157(3):330-40.
19. Luo J, Song W, Yang G, et al. Compound Danshen (*Salvia miltiorrhiza*) dripping pill for coronary heart disease: an overview of systematic reviews. *Am J Chin Med.* 2015;43(1):25-43.
20. Gibbons RJ, Miller TD. Optimal Medical Therapy for Known Coronary Artery Disease: A Review. *JAMA Cardiol.* 2017;2(9):1030-5.
21. Weisz G, Farzaneh-Far R, Ben-Yehuda O, et al. Use of ranolazine in patients with incomplete revascularization after percutaneous coronary intervention: design and rationale of the Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention (RIVER-PCI) trial. *Am Heart J.* 2013;166(6):953-959
22. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol.* 1995;25(2):333-41.
23. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. *Eur Respir J.* 1997;10(11):2662-89.
24. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. 2010;122(2):191-225.
25. Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med.* 1970;2(2):92-8.
26. Gibbons LW, Mitchell TL, Gonzalez V. The safety of exercise testing. *Prim Care.* 1994;21(3):611-29.
27. Baber N. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). *Br J Clin Pharmacol.* 1994;37(5):401-4.
28. Jolicoeur EM, Cartier R, Henry TD, et al. Patients with coronary artery disease unsuitable for revascularization: definition, general principles, and a classification. *Can J Cardiol.* 2012;28(2 Suppl):S50-9.

29. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol.* 1997;30(1):260-311.

## Figures

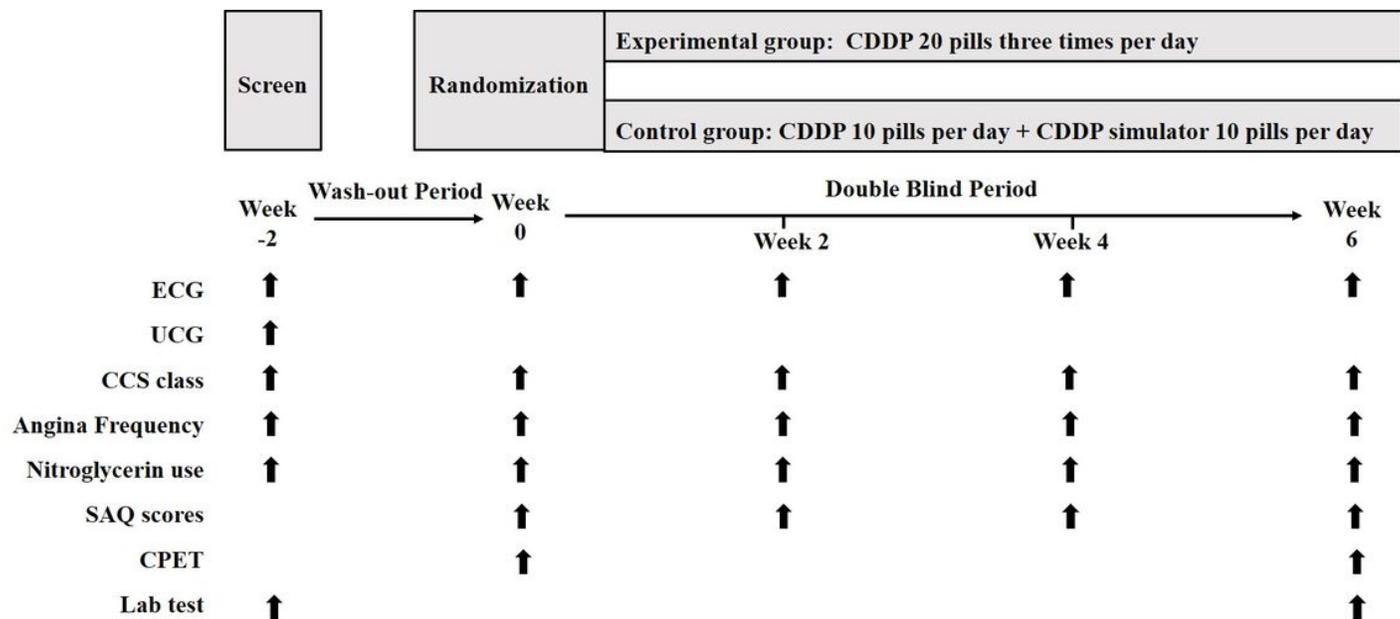


Figure 1

Study design. CDDP, Compound Danshen Dripping Pills; ECG, electrocardiogram; CCS, Canadian Cardiovascular Society; SAQ, Seattle Angina Questionnaire; CPET, cardiopulmonary exercise testing.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SPIRITResearchChecklist.doc](#)
- [Supplementarytable1.INCODERstudy.docx](#)