

# Recommendations on the Clinical Use of Compound Danshen Dripping Pills

Writing Group of Recommendations of Expert Panel from Chinese Geriatrics Society on the Clinical Use of Compound Danshen Dripping Pills

**Key words:** Coronary Heart Disease; Diabetes Complications; Drug Effects; Fufang Danshen; Treatment

## INTRODUCTION

Currently in China, about 290 million people have cardiovascular disease (CVD). Cardiovascular-relevant morbidity and mortality in Chinese population rose quickly, and increasing number of the patients has brought about a serious health problem to the society. CVD has become the leading cause of death in China, and among the overall mortality, two in every five patients have CVD. Fortunately, Chinese patent medicines play an ever-increasing role in the prophylaxis, treatment, and emergency therapy of CVDs. Compound Danshen dripping pills (CDDPs) have been prescribed in short- or long-term administration for more than 450 million patients cumulatively since it came into the market in 1994, and in the past 22 years, CDDPs have been widely used in clinical practice, and valuable experiences have been accumulated. To better understand the rational use of CDDPs, an Ad Hoc Working Group made up of an expert team across the country led by the Chinese Geriatrics Society of the Chinese Medical Association worked out a draft of Recommendations on the Clinical Use of CDDPs. These recommendations are developed mainly on the basis of scientific evidence and expert practical experience, designed to provide physicians with a medication reference rather than providing standards or norms for medical practice. It will be regularly updated when new evidence of CDDPs becomes available.

## ACTIVE INGREDIENTS, PHARMACOKINETICS, CLINICAL PHARMACOLOGY, AND THE ADVANTAGE OF DOSAGE FORM OF COMPOUND DANSHEN DRIPPING PILLS

### Active ingredients of compound Danshen dripping pills

CDDPs contain three medicinal herbs, *Salvia miltiorrhiza*, notoginseng, and borneol. Its active pharmacodynamic

substances consist mainly of phenolic acids (tanshinol, protocatechualdehyde, salvianolic acids U, T, and D, rosmarinic acid, salvianolic acids B and A, all of which are recognized as the peaks No. 1–8 on the reference fingerprints, respectively), saponins (notoginsenoside R, ginsenosides Rb<sub>1</sub>, Rg<sub>1</sub>, and Re, etc.), and borneol. Among those, salvianolic acids U and T are the characteristic active ingredients of CDDPs.<sup>[1]</sup> In the Chinese Pharmacopoeia, each of the above-mentioned three main ingredients of CDDPs is subject to the quality control standards. All the raw materials of *S. miltiorrhiza*, notoginseng, and borneol used for CDDP production are subject to analytical quality control in accordance with the Chinese pharmacopoeia to ensure stable and high-quality standards.<sup>[1]</sup>

### Pharmacokinetic studies of compound Danshen dripping pills

Several pharmacokinetic studies of CDDPs have been published since 2000.<sup>[2-6]</sup> Following the administration of clinical and nonclinical studies of CDDPs to either rats or healthy volunteers, Tanshinol and its main metabolite 4-hydroxy-3-methoxyphenyllactic acid,<sup>[3]</sup> protocatechualdehyde and its main metabolite protocatechuic

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acid,<sup>[4]</sup> notoginsenoside R<sub>1</sub>, and ginsenosides Rg<sub>1</sub> and Rb<sub>1</sub><sup>[5]</sup> were detectable in the blood samples. Among those, T<sub>max</sub> for tanshinol, metabolite 4-hydroxy-3-methoxyphenyllactic acid, protocatechuic acid, notoginsenoside R<sub>1</sub>, and ginsenoside Rg<sub>1</sub> were all <1 h, indicating that CDDP was absorbed very rapidly after its oral administration, while a moderate absorption rate for ginsenoside Rg<sub>1</sub> was observed with a relatively longer half-life, maintaining a sustainable clinical effectiveness.<sup>[6]</sup>

### Pharmacologic effects of compound Danshen dripping pills

CDDP is composed of the mixed extracts of *S. miltiorrhiza*, notoginseng, and borneol. Modern pharmacological studies have demonstrated that CDDP has the following pharmacologic effects: (1) anti-oxidative, anti-inflammatory, and endothelium-protective effects,<sup>[7-9]</sup> inhibition of atherosclerotic plaque formation and neointimal hyperplasia;<sup>[10,11]</sup> (2) reduction of myocardial oxygen consumption,<sup>[12]</sup> improving energy metabolism,<sup>[13]</sup> and protection of cardiomyocytes; (3) inhibition of platelet adhesion and aggregation;<sup>[14-17]</sup> and (4) improvement of microcirculation,<sup>[18,19]</sup> which is known to have beneficial effects in the prevention and treatment of ischemic reperfusion injury,<sup>[20-22]</sup> injury induced by lipopolysaccharide and other microcirculation disturbances.<sup>[23]</sup> Among them, *S. miltiorrhiza* extracts have positive effects on antiperoxidative damage, myocardial protection, myocardial energy metabolism improvement, and antiplatelet aggregation activities. Notoginseng extracts have an effect of anti-coagulation, anti-inflammation, and inhibition of lipid deposition and platelet aggregation. In traditional Chinese medicine theory, there exist complementary and synergistic therapeutic effects following the combination of *S. miltiorrhiza* and notoginseng. Borneol, as an adjuvant and guiding drug, promotes the entry of active ingredients of *S. miltiorrhiza* and notoginseng into the body tissues and organs, and has coronary-dilating and analgesic effects.<sup>[24]</sup>

### Advantages of dosage form for compound Danshen dripping pills

Dripping pill is a solid dispersion product derived from a combination of the drug product and matrix through melt dispersion, dripping, and consolidation. The hydrophilic matrix of CDDP contributes to the rapid drug dissolution and immediate release of the drug substance and rapid onset of action.

The manufacturing process of CDDP, in which the compound uniformly distributes in the melted PEG-6000 matrix, ensures that the drug is completely dissolved within 5–7 min, which is far ahead of the limit requirement of <60 min as defined by Chinese Pharmacopeia.<sup>[1]</sup>

CDDP is more suitable for sublingual administration due to its high drug loading, small dose, and hydrophilicity. The pharmacodynamic ingredients are likely to be directly absorbed through the mucosa into the blood stream when sublingually administered, avoiding hepatic first-pass effect and degradation by digestive juice in the gastrointestinal

tract, and facilitating bioavailability and a rapid relief during emergency condition.

## CLINICAL STUDIES OF COMPOUND DANSHEN DRIPPING PILLS

### Treatment of coronary heart disease

#### Phase II clinical trials of compound Danshen dripping pills for the treatment of angina pectoris of coronary heart disease

*Phase II clinical trials completed in China*

One hundred and fifty-seven patients with angina pectoris of coronary heart disease (CHD) who were eligible for the inclusion criteria defined in accordance with the “clinical guidelines” were enrolled and randomized into two groups in a ratio of 2:1. One hundred and seven patients were treated with CDDP 10 pills three times per day, and fifty patients as a control group were treated with three compound Danshen tablets three times daily, for 2 weeks. The significant therapeutic effective rate in the CDDP group was 35.5%, compared to 20% in the control group ( $\chi^2 = 3.863$ ,  $P < 0.05$ ); while the overall therapeutic effective rates in CDDP group and in the control group were 95.3% and 76%, respectively ( $\chi^2 = 13.164$ ,  $P < 0.01$ ).

*Phase II clinical trials completed in the USA*

CDDP is the first composite formulation of traditional Chinese medicine that has successfully completed Phase II clinical trial under the Food and Drug Administration (FDA)’s Investigational New Drug (IND) Application worldwide. In this study, a total of 125 patients with moderate chronic stable angina pectoris were enrolled at 15 medical centers across the USA. Enrolled patients were randomly assigned to one of the following three treatment arms: placebo, low or high dose group (0, 20 pills, or 30 pills, twice daily), while all the other concurrent medications for angina pectoris were discontinued (with a 14 days washout period) except for on-demand short-acting nitrates and one beta-blocker or calcium channel blocker. The treatment course was 8 weeks. There was a clear dose-response relationship with respect to 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 (low dose group,  $P = 0.18$ ) and 43 s (high dose group,  $P = 0.005$ ). No serious adverse drug reactions (ADRs) were observed, which suggested that CDDP was effective and safe for the treatment of angina pectoris of CHD.

#### Meta-analysis of compound Danshen dripping pills for the treatment of coronary heart disease

Sixteen meta-analysis reports about CDDP used for the prevention and treatment of CHD (involving stable angina pectoris, unstable angina pectoris, myocardial infarction, etc.) have been published, involving 513 original studies with a total of 53,350 patients. All the 16 meta-analysis reports demonstrated positive efficacy and safety profiles of CDDP.<sup>[25-40]</sup> In one meta-analysis involving 16 randomized controlled trials for the indication of angina pectoris with a total of 1802 patients, CDDP was compared to isosorbide

dinitrate in terms of improving symptomatic anginal attacks and electrocardiogram (ECG) findings defined as effective parameters. The results showed that CDDP was more effective than isosorbide dinitrate for relieving anginal pectoris and improving ECG (both  $P < 0.001$ ).<sup>[25]</sup> In a meta-analysis study which involved ten randomized controlled trials, 1037 patients were included and treated for 4–24 weeks. The results demonstrated that CDDP could significantly relieve angina pectoris of CHD and improve ischemia on ECG and could reduce plasma cholesterol and triglyceride levels (all  $P < 0.001$ ).<sup>[26]</sup>

#### **Use of compound Danshen dripping pills in perioperative period of percutaneous coronary intervention**

In a randomized controlled clinical trial involving 500 patients with acute ST segment elevation myocardial infarction who were scheduled for percutaneous coronary intervention (PCI) in the CDDP group, CDDP was administered at a single dose of 20 pills immediately before the procedure and postoperative administration at a dose of 10 pills, three times per day for 30 days, as an add-on to conventional therapy. The results showed that the treatment group had a significantly higher left ventricular ejection fraction ( $P = 0.046$ ) and a significantly lower incidence of ventricular aneurysm ( $P < 0.05$ ), postoperative chest pain ( $P < 0.01$ ), postoperative arrhythmia, and hospitalization arrhythmia ( $P < 0.05$ ) than that in the control group, which demonstrated that CDDP could significantly alleviate postoperative myocardial ischemia, enhanced myocardial blood flow and microcirculation, and reduced postoperative arrhythmia.<sup>[41]</sup>

CDDP was initialized on the day of hospital admission at a dose of 20 pills, three times per day for 3 days, followed by a reduced dose of 10 pills, three times per day for 30 days. The treatment group had significantly lower levels of creatinine, high-sensitivity C-reactive protein, and cystatin C at postoperative 24 h and 48 h than that in the control group ( $P < 0.05$ ). The treatment group had a significantly lower level of homocysteic acid at postoperative 24 h than that in the control group ( $P < 0.05$ ). These results demonstrated that CDDP had certain protective effects on renal function following PCI and had prophylactic and therapeutic effects on radiographic contrast nephropathy.<sup>[42]</sup>

#### **Improvement effect of compound Danshen dripping pills on platelet reactivity when combined with aspirin and clopidogrel**

In a meta-analysis of 24 studies regarding the concomitant use of CDDP and aspirin for the treatment of angina pectoris of CHD, a total of 2275 patients were included. The results demonstrated that CDDP in combination with aspirin for the treatment had obvious advantages over aspirin alone ( $P < 0.001$ ) and had obvious advantages in the improvement of low-density lipoprotein levels ( $P < 0.001$ ).<sup>[43]</sup>

One hundred and two patients with unstable angina pectoris were randomized into three groups: CDDP group ( $n = 33$ ), clopidogrel group ( $n = 35$ ), and combination group ( $n = 34$ ). CDDP (10 pills, three times a day) was administered for

3 weeks in both CDDP group and combination group. The combination group had a significantly lower platelet aggregation rate and thromboxane B<sub>2</sub> levels than that in the other two groups ( $P < 0.05$ ). The results showed significant superiority of CDDP in combination with clopidogrel to either CDDP or clopidogrel alone in anti-platelet aggregation.<sup>[44]</sup>

#### **Compound Danshen dripping pills for the treatment of silent ischemia and microcirculatory angina pectoris**

One hundred and twenty elderly patients with silent ischemia were randomized to receive CDDP in the treatment group and isosorbide dinitrate in the control group. The patients in both groups were treated for 1 month. Heart rate, frequency of ST segment depression, and cumulative time of ST segment depression in both groups had significantly decreased after the treatment. There were significant improvements in CDDP group than that in the control group ( $P < 0.05$ ).<sup>[45]</sup>

Eighty patients with cardiac syndrome X were randomly assigned to the CDDP group ( $n = 40$ ) and control group ( $n = 40$ ). The patients in the treatment group received CDDP as an add-on to conventional therapy. Both groups were treated for 6 weeks. Compared to the control group, CDDP group had higher effective rate for relieving angina pectoris and improving ECG ( $P < 0.05$ ). Endothelin-1 level decreased and nitrogen monoxidum level increased in both groups after treatment. However, this effect was more obvious in observation group with a statistically significant difference ( $P < 0.05$ ). These results showed that CDDP could significantly reduce myocardial ischemia and might improve vascular endothelial function<sup>[46]</sup> in patients with cardiac syndrome X.

#### **Use of compound Danshen dripping pills to relieve acute onset of angina pectoris**

Clinical studies have proved that CDDP can be used to relieve angina pectoris with better effect as an add-on to conventional therapy.<sup>[47,48]</sup>

#### **Prevention and management of diabetes and its complications**

##### **Compound Danshen dripping pills have inhibitory effects on intima-media thickness in diabetic patients**

Five hundred and ninety-nine patients with type 2 diabetes for <1 year were randomly divided into the treatment group ( $n = 296$ ) and the control group ( $n = 303$ ). CDDPs, 10 pills, three times a day were administered as an add-on to antidiabetic, antihypertensive, and antilipemic therapies in the treatment group while conventional therapy alone was administered in the control group. For the treatment group, the intima-media thickness (IMT) of the carotid arteries was  $0.74 \pm 0.14$  mm at predose and  $0.74 \pm 0.19$  mm at postdose after 2 years treatment as compared with  $0.73 \pm 0.15$  mm and  $0.76 \pm 0.19$  mm, respectively, for the control group, and there were significant differences between the two groups at postdose ( $P < 0.05$ ). For the treatment group, the IMT

of the carotid arteries was  $0.74 \pm 0.14$  mm at pretreatment and  $0.74 \pm 0.19$  mm at posttreatment after 2 years treatment as compared with  $0.73 \pm 0.15$  mm and  $0.76 \pm 0.19$  mm, respectively, for the control group ( $P < 0.05$ ). These results demonstrated that CDDP had protective effects on early-stage atherosclerosis.<sup>[49]</sup>

One hundred and thirty patients with newly diagnosed diabetes were randomized to receive antidiabetic and antihypertensive therapies in Group A ( $n = 32$ ); antidiabetic, antihypertensive, and antilipemic therapies in Group B ( $n = 32$ ); antidiabetic, antihypertensive, and antilipemic therapies plus Vitamin E in Group C ( $n = 32$ ); and antidiabetic, antihypertensive, and antilipemic therapies plus CDDP, 10 pills, three times per day in Group D ( $n = 34$ ). All the patients were treated for 5 years. The IMT of the carotid arteries gradually increased in each group as compared with predose (all  $P < 0.05$ ). However, Group D had a significantly delayed development in the IMT ( $P < 0.01$  vs. Group A, both  $P < 0.05$  vs. Groups B and C) and a significantly lower incidence of intima-media abnormalities of the carotid arteries and plaques (all  $P < 0.05$ ) than that in the other groups, which demonstrated that CDDP could delay the development and progression of diabetic macroangiopathy.<sup>[50]</sup>

In a multicenter randomized controlled clinical trial involving 744 patients with type 2 diabetes for more than 3 months, background therapy (conventional oral antidiabetics + statins) was administered in the control group and background therapy + CDDP 15 pills, three times per day, were administered in the treatment group. All the patients were treated for 24 weeks. The efficacy was evaluated using semi-quantitative scores. The treatment group had a significantly greater response rate (84.38%) than that in the control group (73.33%,  $P < 0.05$ ). In addition, mean serum matrix metalloproteinase 9 was significantly reduced at postdose stage compared to that at predose period ( $P < 0.01$ ). Reductions in carotid artery IMT and plaque area were observed in both groups ( $P < 0.05$  or  $P < 0.01$ ), but there was lower thickness of carotid artery IMT in the CDDP treatment group than that in the control group ( $P < 0.05$ ). These results demonstrated that CDDP improved the severity of arteriosclerosis in vasculopathy in type 2 diabetes and reduced carotid artery IMT. Therefore, it was considered that CDDP showed a potential protective effect for blood vessels.<sup>[51]</sup>

#### **Therapeutic effects of compound Danshen dripping pills on diabetic retinopathy**

In a randomized, double-blind, dose parallel, controlled, multicenter clinical trial involving 223 patients with nonproliferative diabetic retinopathy, patients received CDDP treatment at high dose (30 pills three times per day), moderate dose (20 pills three times per day), low dose (10 pills three times per day), and placebo. Fluorescence fundus angiography was performed at postdose 24 weeks, which showed that the ratio of “complete response rate” to “partial response rate” was 74% and 77%, respectively. With

high and moderate doses, response rate was significantly greater than that for the placebo group (28%,  $P < 0.001$ ). The examination of ocular fundus showed that the ratio of “complete response rate” to “partial response rate” was 42% and 59%, respectively, for the high and moderate doses and was significantly greater than that for the placebo group (11%,  $P < 0.001$ ). No statistically significant adverse events were observed throughout the study.<sup>[52]</sup>

In a meta-analysis involving 17 randomized controlled studies, CDDP, as a main intervention, was used for the treatment of diabetic retinopathy in 1050 patients. The dosage of CDDP was 10 pills, three times a day. The results showed that the treatment group had significantly superior overall efficacy ( $P < 0.01$ ) and better effects on visual acuity, vision gray value, number of hemangiomas, and area of bleeding lesions when compared with the control group (all  $P < 0.01$ ).<sup>[53]</sup>

#### **Therapeutic effects of compound Danshen dripping pills on diabetic nephropathy**

So far, three papers on meta-analysis including 47 literatures have been published with 3574 patients on the use of CDDP for the prevention and treatment of diabetic nephropathy. The results showed that CDDP significantly reduced microalbumin excretion rate and 24-h urine protein quantitation. Moreover, total cholesterol and triglyceride also declined following CDDP treatment. In addition, CDDP showed good safety profiles.<sup>[54-56]</sup>

In a meta-analysis of 19 randomized controlled clinical trials involving 1491 patients, CDDP group ( $n = 740$ ) received conventional therapy plus CDDP 10 pills, three times per day, and the control group ( $n = 751$ ) received conventional therapy alone. All the patients were treated for 4–36 weeks. The results showed that the CDDP group had a significantly higher total response rate ( $P < 0.05$ ) than that in the control group, suggesting that CDDP significantly reduced microalbumin excretion rate and 24-h urine protein quantitation (both  $P < 0.01$ ) than that in the control group. The results also showed that CDDP could significantly reduce urine protein level and could be used as an add-on treatment for diabetic nephropathy.<sup>[54]</sup>

In another meta-analysis of 14 randomized controlled trials involving 1050 patients, the CDDP combination group had a significantly lower urine microalbumin excretion rate at postdose ( $P < 0.001$ ). The differences in liver function (alanine transaminase and aspartate transaminase) between pre- and post-dose were statistically insignificant. These results showed that CDDPs were highly effective and safe for the treatment of diabetic nephropathy, without any significant effects on liver function.<sup>[55]</sup>

## **SAFETY PROFILE OF COMPOUND DANSHEN DRIPPING PILLS**

In the past two decades of its marketing, the safety files of CDDP have been proved through the application by

hundreds of millions of people and more than tens of thousands of literature reports. The adverse reactions, with most spontaneous remission, were merely occasional gastrointestinal discomfort, head fullness sensation, and facial flushing.

Multiple nonclinical safety evaluations were performed for CDDP in both the pre- and post-marketing periods, which demonstrated its good safety profile in long-term treatment due to the broad safety window. The maximum tolerated doses for acute oral toxicity tests in rats were 26.7 g of drug product/kg. The no-observed-adverse-effect-level (NOAEL) for 6 months long-term toxicity tests in rats was 4 g of crude drug/kg whereas the NOAEL for 9 months long-term toxicity tests in Beagles was 2.5 g of drug product/kg, which were completed during the postmarketing period and FDA new drug approval application. Reproductive toxicity and developmental toxicity tests in rats were also performed, showing a safety window with the NOAEL of 1.5 g of drug product/kg, 4 g of drug product/kg, and 4 g of drug product/kg in Phase I, II, and III tests, respectively. No mutagenicity was noted in Ames test, rat micronucleus test, and carcinogenesis studies.<sup>[56]</sup> No inhibitory effects were observed when co-incubated *in vitro* with CYP4501A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. Borneolum syntheticum, widely used in clinical practice, particularly in the treatment of CVDs and encephalopathy, is a common aroma-resuscitating drug. Relevant studies have shown that borneol was safe without obvious long-term toxicity and reproductive toxicity<sup>[57]</sup> or mutagenicity.<sup>[58]</sup>

In a Phase II clinical study conducted in 107 patients with angina pectoris of CHD, one patient developed mild nausea after each dose, which disappeared 15 min later. Head fullness sensation, which only lasted for a short period of time, was observed in very few patients, and there was no need to discontinue the treatment. In a Phase II clinical study conducted in patients with diabetic retinopathy, no drug-related adverse events were observed, with two, three, one, and four cases of minor adverse reactions in the placebo group, high, moderate, and low dose groups, respectively. No statistical significance was shown among the groups.<sup>[52]</sup>

In a Phase II clinical trial conducted under the FDA IND in the US, there was no statistically significant difference in adverse events among the three groups. Most adverse events were mild in intensity and were unrelated to the treatment. No drug-related serious adverse events were reported. The adverse events related to CDDP were merely mild gastrointestinal symptoms, such as abdominal distention and dyspepsia. Mild facial flushing and head fullness sensation were observed occasionally, which were consistent with those reported in the long-term clinical application in China. In addition, QTc analysis showed that CDDP had good cardiac safety profiles.

Relevant literatures on the combination of CDDP with antiplatelet drugs such as aspirin and clopidogrel<sup>[43-45]</sup> have demonstrated its good safety profiles without an increased risk of side effects such as bleeding.

A total of 1413 adverse reactions/events related to CDDP were received by China FDA (CFDA) Center for ADR. Through the observation from January 1, 2011 to September 30, 2014 (a total of 79,497,137 patients in the required course of medication, with incidence rate of 0.0018%), adverse reactions were listed as follows in the order of frequency: gastrointestinal symptoms (stomach ache, nausea, eructation, sour regurgitation, hiccups, stomach discomfort, dyspepsia, diarrhea, and abdominal distension), discomfort, nonspecific hemorrhage, nonspecific purpura, local numbness, abnormal bowel sounds, headache, chest distress, dry mouth, palpitation, weakness, flushing, hyperhidrosis, etc. Among them, there were 18 cases with serious adverse reactions/events, five of which were related to inappropriate medication (two cases of cataract, one case of myocarditis, and one case of hypertension), and the rest were considered to be related to primary diseases. The above adverse reactions/events were all cured or improved.

## RECOMMENDATIONS FOR CLINICAL USE OF COMPOUND DANSHEN DRIPPING PILLS

### Compound Danshen dripping pills are recommended for the following clinical indications

1. Long-term treatment with CDDP as an add-on to standard therapy in patients with angina pectoris of coronary origin, as well as nitrate intolerance, low or no response to aspirin or clopidogrel treatment, reduced exercise tolerance, perioperative period of PCI, and silent ischemia and cardiac syndrome X
2. Chinese patent medicine in the emergency treatment of angina pectoris of CHD
3. Add-on to conventional therapy in diabetic patients for the prevention and treatment of diabetic vascular complications
4. Improvement effect of CDDP on platelet reactivity when combined with aspirin and clopidogrel.

### Posology and method of administration of compound Danshen dripping pills

1. For treatment of CHD, the recommended dose is 10 pills, three times per day, orally or sublingually. The treatment course is 4 weeks and it can be prolonged according to the patient's condition
2. For emergency treatment of angina pectoris in the attack of angina pectoris, the recommended dose is 10 pills, sublingually. Another ten tablets or treatment with nitrates can be administered if the symptoms persist within 5 min
3. For the treatment of diabetic microvascular complications, the recommended dose is 10–20 pills, three times per day, orally or sublingually. The length of the course is 24 weeks and it can be prolonged according to patient's condition
4. CDDP is recommended to be sublingually administered or orally 30 min after meal for patients with stomach discomfort.

## Contraindication

Unknown.

## Precautions

Pregnant women must be cautious about using the drug.

## Adverse drug reaction

There was occasional discomfort in the gastrointestinal tract.

## CONCLUSION

CDDPs are a Chinese patent medicine that plays an ever-increasing role in the prophylaxis, treatment, and emergency therapy of CVDs. The contents of three active main ingredients of CDDP are stable and absorbed very rapidly after oral administration. With its high efficiency and safety observed in clinical practice, CDDP is recommended for long-term treatment as an add-on to standard therapy in patients with angina pectoris of coronary origin, as well as nitrate intolerance, low or no response to aspirin or clopidogrel treatment, reduced exercise tolerance, perioperative period of PCI, and silent ischemia and cardiac syndrome X; in the emergency treatment of angina pectoris of CHD; add-on to conventional therapy in diabetic patients for the prevention and treatment of diabetic vascular complications.

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## Conflicts of interest

There are no conflicts of interest.

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