

The Safety and Tolerance of Herbal Anti-Angina Drug Compound Danshen Droplet Pill in Healthy Volunteers

Ying Zhou¹, Yimin Cui^{1*}, Xia Zhao¹, Yong Huo², Zhaohong Nie^{3,4}, Min Zhao^{3,4}, Zhixin Guo^{3,4}, He Sun^{3,4}

¹Department of Pharmacy, Peking University First Hospital, Beijing, China; ²Department of Cardiology, Peking University First Hospital, Beijing, China; ³Tasly Pharmaceutical Group Co., Ltd., Tianjin, China; ⁴Suntech Research Institutes, Rockville, USA.
Email: *cuiymzy@126.com

Received June 19th, 2013; revised July 25th, 2013; accepted August 16th, 2013

Copyright © 2013 Ying Zhou *et al.* This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Compound Salvia Pellet (T89), consisting of Danshen (*salvia miltiorrhiza*), Sanqi (*panax notoginseng*), and Borneol (*Cinnamomum camphora*), has been used worldwide for 14 years for chronic angina treatment. **Purpose:** A dose escalation study to determine the maximum tolerance dose (MTD) in Chinese population to support a proposed dose regimen change. **Methods:** Forty-six participants (age 18 to 45 yrs, male to female ratio = 1:1) were divided into a series of 6 patients cohorts, and sequentially assigned into one of the escalating dose groups, starting from 540 mg, the clinical doses, until 4 out of 6 subjects experience clinical Adverse Events (AEs) or when the pre-defined 3510 mg dose level is reached and completed. All doses were given orally as a single dose 2 hours after breakfast. Adverse events, vital signs, 12-lead ECG, clinical and laboratory parameters and medical evaluation were conducted as outcome measures. **Results:** Study completed at the highest pre-defined dose level of 3510 mg dose as never had 4/6 of subject experience AEs in any dose levels studied. All participants completed the study and data were included in the safety analysis. The only moderate AE observation (muscle damage) was observed at 2970 mg dose and was recovered without any medical treatment, and all other AEs (ECG, dizziness, muscle damage) were mild and may (5 cases) or may not (9 cases) be related to testing drug and were all self-resolved within 30 min after dose. **Conclusion:** Given as single oral dose, Compound Salvia Pellet is safe and well-tolerated up to the 3510 mg studied. The MTD value of Compound Salvia Pellet is unknown from this trial and must be higher than 3510 mg, 13 times higher than its current clinical dose.

Keywords: Compound Salvia Pellet; Safety; Tolerance; Chronic Angina Treatment

1. Introduction

Compound Salvia Pellet (T89), has been widely used in China for 14 years, and used worldwide for more than 10 years. Compound Salvia Pellet is indicated for chronic angina treatment [1,2], manufactured and marketed by Tianjin Tasly Group Co., Ltd of P. R. China. T89 has been marketed as composite Danshen pill [3], Compound Danshen droplet pill [4], or Cadiotonic Pill, and Dantonic Dripping pills. It is an herbal drug consisting of active herbal ingredients co-extracted from Danshen (*salvia miltiorrhiza*) and Sanqi (*panax notoginseng*), and tiny amount of Borneol (*Cinnamomum camphora*) [3]. According to Traditional Chinese Medicine (TCM) concept, *salvia miltiorrhiza* in this formula, which is regarded as the principal drug (known as the “King drug”), can promote or invigorate blood flow and remove blood stasis.

Experimental studies have shown that *salvia miltiorrhiza* can dilate coronary arteries, increase coronary blood flow [5], and scavenge free radicals [6] in ischemic diseases, so that it reduces the cellular damage from ischemia and improves heart functions. *Panax notoginseng* serves as “the Minister drug” to reinforce *salvia miltiorrhiza*’s therapeutic action, which can inhibit activation of platelets and their adhesion and aggregation [7], and counteract free-radical damage associated with atherogenesis [8,9]. *Cinnamomum camphora*, for resuscitation, is related to the heart channel and lung channel, to “open and revive the spirit” according to TCM. Clinical studies demonstrated that T89 has numerous clinical effects on increasing coronary flow rate and superoxide dismutase activity, expanding the blood vessel, promoting blood circulation, relieving blood stasis, improving the microcycle and changing the blood viscosity, also decreasing the consuming oxygen of the cardiac muscle, with the

*Corresponding author.

effects on anticancer, antibacterial, antiinflammation, etc. [10-12].

A meta-analysis suggests that compound salvia pellet is safe and does not develop tolerance over time [13]. However, most of the included trials were using lower dose levels. Especially, the worldwide commonly used clinical dosage of T89 is 270 mg each time, 3 times a day, regardless of race, age, and body weight.

In 10 years of post-marketing safety watch, Composite Salvia Dropping Pill showed none severe adverse reaction. Meanwhile, clinicians frequently use higher dose in clinical practice. Based on preclinical studies sponsored by Tasly *Pharmaceutical Group*, the LD50 in mice after single dose is 16.7 mg/kg (Is it 16.7 mg or 16.7 mg/kg? Is the number correct?). The result of long term toxicity test indicates that the highest dosage among the three testing groups used in this animal study is the 50 times higher than human common dose.

The objective of this dose escalation study was to estimate the MTD in Chinese population to support a proposed dose regimen change.

2. Materials and Methods

2.1. Study Drug Administration

Clinical trial material (CTM) was a two herbal mixture extract preparation and was produced and provided by Tianjin Tasly Group Co., Ltd. CTM for the phase I type MTD study was supplied as 27-mg pills. The Batch Number was 20060908.

2.2. Study Design

This randomized, open label, dose escalation study of Composite Salvia Dropping Pill was performed in Chinese healthy volunteers. A total of 46 healthy, nonsmoking volunteers, 18 to 45 years of age (difference is not fit to be 10 years in the same group (I cannot understand this sentence, please revise)) and with body mass index (BMI) between 19.0 and 25.0 kg/m². All participants were able to give written informed consent before to be enrolled in the study, same numbers of male and female subjects were enrolled to ensure gender balance. The study was conducted in according with Good Clinical Practice and International Council on Harmonization guidelines. The study protocols and the informed consent were approved by the Clinical Drug Trial Ethical Committee of the Peking University First hospital. Study personnel obtained written informed consent directly from all subjects prior to their entry into the study.

The nine single doses of T89 evaluated were 20, 40, 60, 70, 80, 90, 100, 120, and 130 pills of the 27 mg formulation. The doses were administered orally with 500 mL warm water 2 hours before meal. All subjects were randomly divided into 9 groups, 6 subjects per group.

Volunteers were admitted to the study unit the day before each scheduled dosing period and remained at the study site for 24 hours after dosing. Does escalation were started from the lowest dose, and move to the next dose until all safety profile were checked and observed. Each subject only took one dose and was not repeated for any other dose level. The stopping criteria for dose escalation was that if testing drug related adverse reaction were observed in 4/6 subjects, the same dose will be repeated. If the same or higher frequency of adverse reaction was observed again, MTD will be defined as the dose that is one level lower. If adverse reaction rate was lower than 4/6 in the repeated dose level, dose escalation will continue to move to a higher dose. All dose groups were monitored on a combined inpatient/outpatient basis. During the one week outpatient period, subjects reported daily to the study unite for scheduled events and procedures.

2.3. Safety and Tolerability Evaluations

The tolerability and safety of T89 were evaluated based on adverse-event reports, vital signs, electrocardiograms, clinical laboratory values, and results of physical examination. Study subjects were monitored carefully throughout each dosing period for adverse experiences. The relationship of adverse events to the study drug was assessed by a qualified physician and is in general based on such considerations as temporal relationship to study drug administration, subject's relevant medical history, and whether the finding is likely due to any pre-existing conditions.

Electrocardiograms monitoring was performed using Twelve-lead ECG (PHILIPS Page Writer Trim III, USA Philips Co. Ltd.). The measurements were made at the first screening visit, pre-administration, 0.5, 1, 2, 3, 4, 6, 8, 24 h and 7 d after test drug administration and any other time if necessary. Except for adverse events, 12-lead ECG, vital signs and clinical laboratory, including CK, CK-MB, HBDH, CTN I were evaluated.

2.4. Statistics

A paired t test was used to evaluate the safety data within each group (within each group or for each subject?), and P-values of less than 0.05 were considered as statistically significant.

3. Results

3.1. Enrollment and Demographics

A total of 46 Chinese male or female healthy subjects were enrolled in the study with the age of 26 to 39 years, 22 males and 24 females. Subjects for these study were similar in age (35.1 ± 3.43 years); weight (60.0 ± 8.25

kg); height (1.62 ± 0.079 m); and body mass index (22.8 ± 1.92) (**Table 1**).

As shown in **Table 1**, 9 of the subjects were current smokers. All smoking subjects were aged between 20 and 25, except for subject 120 who was 19 upon screening. This subject was discontinued from the study upon discovery of that he started smoking was outside the age range for inclusion criterion. The average height of all subjects was 171 cm (range: 163 - 183 cm), with an average weight of 65.3 kg (range: 53.0 - 82.0 kg). The BMI ranged between 19.2 - 27.0 kg/m² with a mean of 22.4 kg/m².

3.2. Safety Observations

Safety was monitored at 0.5, 1, 2, 3, 4, 6, 8, 24 h and 7 days postdose. Adverse events (ADR) in all dose levels were recorded. All participants completed the study and were included in the safety data analysis. Any clinically significant change in laboratory values post drug administration compared to baseline were recorded as ADR and are summarized in **Table 2**.

Overall, during the course of the study, there was no significant change in vital signs when compared to pre-dose baseline. Specifically, thirteen out of 46 subjects reported a total of 14 treatment-emergent mild or moderate adverse events (all causalities) during the study. Five out of the 14 events were judged by the investigator to be related to study drug, while the other 9 were considered unrelated. All of the reported adverse events were mild except for that the muscle damage was rated as moderate. All the adverse events disappeared spontaneously.

There were no clinically significant ECG findings reported except one case of ST-T change. (Please provide a little more information, such as what types of change, degree, recovery and etc.).

There were also no clinically significant alterations in

laboratory values except one subject showed a single lift of ALT, HBDH, CK, CK-MB, TBIL, TG, WBC, LEU values after the 120 pills dose level. This subject's CK, CK-MB and MB have significant clinical differences 2 days after drug administration. The subject was instructed to take a lot of water after the diagnosis. All the laboratory values were improved 5 days afterwards. Double check on day 11 showed everything are back to normal. **Table 3** summarizes CK, CK-MB, MB and other laboratory values for baseline, day 1 and day 7 for this subject. It can be seen that the CK levels increased after both day 1 and day 7 post dose comparing baseline. However, they were still within the normal range and was not clinically significant alterations.

3.3. MTD Value

Although 120×27 mg dose group had one subject experienced muscle injury with moderate degree, this does not warrant to stop the trial. Next dose of 130×27 mg dose was continued with caution. Neither ADRs, nor CK ascending symptoms were observed in the 130 pills group.

According to pre-defined study protocol, if in the accelerative process, more than 4/6 of the subjects indicate severe adverse reaction directly related to the trial drugs, the acceleration must be stopped and repeated. The trial reached its final termination dose level at 130 pills without any clinical severe adverse reaction. Therefore, the MTD should be greater than 130 pills.

4. Discussion

Chronic stable angina is a major health problem that affects over 7 million adults in the United States, with an estimated 400,000 new cases annually [14], and it results in a considerable burden for both the individual and

Table 1. Subjects studied.

	T89									
	20 × 27 mg group	40 × 27 mg group	60 × 27 mg group	70 × 27 mg group	80 × 27 mg group	90 × 27 mg group	100 × 27 mg group	120 × 27 mg group	130 × 27 mg group	
Total subjects	4	4	4	4	6	6	6	6	6	
Male	2	2	2	2	3	3	2	4	2	
Female	2	2	2	2	3	3	4	2	4	
Age (years)										
Mean	30.8	37.8	34.8	35.3	35.7	33.8	37.3	34.7	36.8	
Range	30 - 32	37 - 38	31 - 38	32 - 38	31 - 38	31 - 39	37 - 38	30 - 39	26 - 39	
BMI (kg/m ²)										
Mean	22.8	23.7	22.9	22.3	22.3	22.2	22.9	23.5	23.1	
Range	20.7 - 24.7	21.7 - 25.0	21.0 - 25.0	21.2 - 23.6	19.5 - 24.4	19.2 - 24.9	19.5 - 25.0	20.1 - 25.0	19.5 - 25.0	
Race										
Asian	4	4	4	4	6	6	6	6	6	

Table 2. Frequency of treatment-emergent drug-related* adverse events by type.

MedDRA term	Number of adverse events [number of subjects with adverse event]								
	20 × 27 mg group (N = 4)	40 × 27 mg group (N = 4)	60 × 27 mg group (N = 4)	70 × 27 mg group (N = 4)	80 × 27 mg group (N = 6)	90 × 27 mg group (N = 6)	100 × 27 mg group (N = 6)	120 × 27 mg group (N = 6)	130 × 27 mg group (N = 6)
Vascular disorders									
abnormal ECG	1 [1]								
Nervous system disorders									
Dizziness		1 [1]		1 [1]					
Dizziness and sweat								1 [1]	
Musculoskeletal and connective tissue disorders									
muscle damage								1 [1]	
Total	1 [1]	1 [1]		1 [1]				2 [2]	

N = Number of subjects; *Adverse events with possible or probable relationship to study drug.

Table 3. Level of clinical laboratory by subjects in 130 × 27 mg group.

Special laboratory (unites)	Reference range	Baseline	Change from baseline to 1d	1 d	Change from baseline to 7 d	7 d
PT (s)	10 - 14	10.5 ± 0.4	-0.6 ± 0.5*	9.9 ± 0.4	-0.2 ± 0.1	10.3 ± 0.4*
APTT (s)	23 - 35	26.3 ± 0.9	0.1 ± 2.2	26.4 ± 1.9	0.8 ± 2.0	27.1 ± 1.8
AST (U/L)	0 - 45	25.3 ± 3.4	-2.5 ± 4.5	22.8 ± 4.2	-6.1 ± 5.6	19.2 ± 2.3*
ALT (U/L)	0 - 40	14.6 ± 5.8	1.6 ± 7.2	16.2 ± 8.6	0.5 ± 9.8	15.1 ± 6.4
CREA (μmol/L)	35 - 97	51.1 ± 11.6	11 ± 14.6*	62.1 ± 13.5	1.1 ± 14.2	52.2 ± 7.8
BUN (μmol/L)	2.9 - 7.2	3.9 ± 0.3	0.5 ± 0.5	4.4 ± 0.7	0.3 ± 1.7	4.2 ± 1.1
GLu (mmol/L)	3.31 - 6.1	5.8 ± 0.9	-0.8 ± 1.0*	5.0 ± 0.2	-0.5 ± 1.2	5.3 ± 0.8
TCHO (mmol/L)	3.1 - 5.66	4.86 ± 0.58	-0.23 ± 0.34	4.63 ± 0.67	-0.57 ± 0.66	4.29 ± 0.64*
TG (mmol/L)	0.14 - 1.8	0.9 ± 0.47	0.58 ± 0.86*	1.48 ± 0.74	0.04 ± 0.82	0.94 ± 0.56
HDL-C (mmol/L)	1.00 - 1.55	1.39 ± 0.18	-0.14 ± 0.25	1.25 ± 0.16	-0.13 ± 0.12	1.26 ± 0.08
LDL-C (mmol/L)	2.1 - 3.1	2.9 ± 0.39	-0.22 ± 0.56	2.68 ± 0.47	-0.37 ± 0.66	2.53 ± 0.42*
MB (ng/ml)	<100	18.75 ± 4.08	-1.32 ± 3.64	17.43 ± 1.58	-3.2 ± 2.89	15.55 ± 3.53
CK (U/L)	24 - 170	123.9 ± 25.6	-49.5 ± 19.2*	74.4 ± 17.4	-25.7 ± 22.9	98.2 ± 17.3*
CK-MB (U/L)	2 - 25	9.5 ± 8.0	-4.1 ± 6.4	5.4 ± 4.2	-3.0 ± 5.4	6.5 ± 4.4

Baseline, change (baseline to 1 d, baseline to 7 d), and 1 d, 7 d, means ± SD, for levels of clinical laboratory by Subjects in 130 × 27 mg Group, the maximum tolerated dose (MTD) group are shown. *p < 0.05, within groups. There were statistically significant differences not clinically significant alterations, still in the normal range.

society. At present, organic nitrates are indicated as the firstline therapy for the long-term management of chronic stable angina [15-18]. Organic nitrates have been prescribed to patients with stable angina in the last 100 years or more and are still widely used in the treatment of such patients. However, some adverse effects have also been reported. The major problem with long-term used of nitroglycerin and long-acting nitrates is development of tolerance. Although in some clinical trials intermittent therapy seems to be a hopeful strategy in preventing nitrate tolerance and has proved superior to continuous therapy [19,20], it still has problems, such as possible association with rebound myocardial ischemia during the

nitrate-free period and adverse effects on performance on treadmill exercise tests during the period of withdrawal from nitrates [16]. In search of better treatment options, many patients in both east and west have turned to alternative medicines in the hopes of identifying "natural" substances with less toxicity but equal effectiveness. T89, as one of the alternative therapies, is widely used in China and worldwide, as drug or dietary supplement, but the best clinical dose to ensure the efficacy and safety of T89 for the treatment of chronic stable angina pectoris needs further investigation. Until now, many randomized controlled trials (RCTs) have been completed or published which indicate that T89 may be effective in

patients with chronic stable angina pectoris compared with the organic nitrates [21]. But most of the included trials were at lower doses or inclusive [13]. This study demonstrated that T89 was well tolerated after administration as a single oral dose across the 20×27 mg to 130×27 mg dose range. Moreover, rigorously designed, multi-center, large, randomized, double-blind, controlled trial is being performed in the USA.

In a retrospective meta-analysis, adverse events were described in 17 of the 27 trials (63.0%). Adverse events were reported in 26 of 1093 (2.4%) patients treated with CSP [13]. Abdominal complaints, nausea, dyspepsia and dizziness were reported most often, and which completely alleviated without any treatment [13,21,22]. Dizziness was the most adverse events that have been reported, and duration prolonged as the dosage ascends. In this trial, the 40×27 mg group, 70×27 mg group, and 120×27 mg group each had one case of adverse event, and the attacking time was about 1 hour to 2 hours after administration with duration of 3 minutes, 7 minutes or 20 hours, accompanied with deficient sweating. It seems the degree of sweating is related to dose. All the three subjects were female, who might be more sensitive to the drugs. The first and only moderate AE (muscle damage) was observed at 120×27 mg dose and were recovered without medical treatment. None CK ascending symptoms occurred in the following 130×27 mg group. However, such observation suggests muscle damage could be observed and should be monitored in case of overdose. The mechanism of muscle damage is waiting to be investigated.

Clinical Tolerance Study usually are conducted before large clinical phase 2 or phase 3 trials. Mice LD₅₀ of single dose was 16.7 mg/kg. Long term toxicity study indicates that highest dose is 50 times higher than human dose. At single oral dose, T89 is safe and well-tolerated up to 130×27 mg dose. The MTD value of T89 in this study was not reached, is unknown, and must be higher than 130×27 mg.

5. Conclusion

In conclusion, T89 was well tolerated after administration as a single dose to across the 20×27 mg to 130×27 mg dose range. T89 was safe and well tolerated at the highest dose level studies: 130×27 mg. The MTD value of T89 was not reached in this trial, which was unknown, and must be higher than 130×27 mg.

REFERENCES

- [1] C.-E. Deng, "Progress on Pharmacological and Clinical Application of *Salvia Miltiorrhiza*," *Lishizhen Medicine and Materia Medica Research*, Vol. 14, No. 12, 2003, p. 776.
- [2] N. Ding, "Research Advancement and Clinical Application of Compound Danshen," *Chinese Traditional and Herbal Drugs*, Vol. 33, No. 12, 2002, pp. 1147-1148. (in Chinese)
- [3] Z. X. Guo, W. Jia, W. Y. Gao, *et al.*, "Clinical Investigation of Composite Danshen Pill for the Treatment of Angina Pectoris," *Chinese Journal of Natural Medicines*, Vol. 1, No. 2, 2003, pp. 124-128. (in Chinese)
- [4] Y. H. Shi, "Comparative Study of Composite Danshen Droplet Pills and Sordid in Treatment of Patients with Chronic Stable Angina," *Zhongguo Zhong Xi Yi Jie He Za Zhi*, Vol. 17, No. 1, 1997, pp. 23-25. (in Chinese)
- [5] W. Zhou and T. J. Ruigrok, "Protective Effect of Danshen during Myocardial Ischemia and Reperfusion: An Isolated Rat Heart Study," *The American Journal of Chinese Medicine*, Vol. 18, No. 1, 1990, pp. 19-24. doi:10.1142/S0192415X90000046
- [6] A. M. Wang, S. H. Sha, W. Lesniak, *et al.*, "Tanshinone (*Salviae miltiorrhizae* Extract) Preparations Attenuate Aminoglycoside-Induced Free Radical Formation: *In Vitro* and Ototoxicity *in Vivo*," *Antimicrobial Agents and Chemotherapy*, Vol. 47, No. 6, 2003, pp. 1836-1841. doi:10.1128/AAC.47.6.1836-1841.2003
- [7] J. Wang, J. Xu, J. B. Zhong, *et al.*, "Effect of Radix Notoginseng Saponins on Platelet Activating Molecule Expression and Aggregation in Patients with Blood Hyperviscosity Syndrome," *Zhongguo Zhong Xi Yi Jie He Za Zhi*, Vol. 24, No. 4, 2004, pp. 312-316. (in Chinese)
- [8] P. Chan, G. N. Thomas and B. Tomlinson, "Protective Effects of Trilinolein Extracted from Panax Notoginseng against Cardiovascular Disease," *Acta Pharmacologica Sinica*, Vol. 23, No. 12, 2002, pp. 1157-1162.
- [9] W. Zhou, H. Chai, P. H. Lin, *et al.*, "Molecular Mechanisms and Clinical Applications of Ginseng Root for Cardiovascular Disease," *Medical Science Monitor*, Vol. 10, No. 8, 2004, pp. RA187-RA192.
- [10] Y.-J. Wu, C.-Y. Hong, S.-J. Lin, P. Wu and M.-S. Shiao, "Increase of Vitamin E Content in LDL and Reduction of Atherosclerosis in Cholesterol-Fed Rabbits by a Water-Soluble Antioxidant-Rich Fraction of *Salvia miltiorrhiza*," *Thrombosis, and Vascular Biology*, Vol. 18, 1998, pp. 481-486. doi:10.1161/01.ATV.18.3.481
- [11] O. Karmin, E. G. Lynn, R. Vazhappilly, K. K. W. Au-Yeung, D.-Y. Zhu and Y. L. Siow, "Magnesium Tanshinolate B (MTB) Inhibits Low Density Lipoprotein Oxidation," *Life Sciences*, Vol. 68, No. 8, 2001, pp. 903-912. doi:10.1016/S0024-3205(00)00989-9
- [12] T. Kyoko, O. Xinshou, K. Katsuko, N. Norio, H. Masao and B. Akemichi, "Sodium Tanshinone IIA Sulfonate Derived from Danshen (*Salvia miltiorrhiza*) Attenuates Hypertrophy Induced by Angiotensin II in Cultured Neonatal Rat Cardiac Cells," *Biochemical Pharmacology*, Vol. 64, No. 4, 2002, pp. 745-750. doi:10.1016/S0006-2952(02)01250-9
- [13] G. Wang, L. Wang, Z. Y. Xiong, B. Mao and T. Q. Li, "Compound *Salvia* Pellet, a Traditional Chinese Medicine, for the Treatment of Chronic Stable Angina Pectoris Compared with Nitrates: A Meta-Analysis," *Medical Science Monitor*, Vol. 12, No. 1, 2006, pp. SR1-SR7.

- [14] P. Mickie, R. Peled, L. Matityhau, *et al.*, "Reasons for Overprescription of Mononitrates: The Paradigm of Stable Angina Pectoris Treatment," *Current Therapeutic Research*, Vol. 64, No. 9, 2003, pp. 662-675. [doi:10.1016/j.curtheres.2003.09.013](https://doi.org/10.1016/j.curtheres.2003.09.013)
- [15] S. P. Glasser, "Clinical Mechanisms of Nitrate Action," *American Journal of Cardiology*, Vol. 81, No. 1, 1998, pp. 49A-53A. [doi:10.1016/S0002-9149\(97\)00998-3](https://doi.org/10.1016/S0002-9149(97)00998-3)
- [16] S. D. Fihn, S. V. Williams, J. Daley, *et al.*, "American College of Cardiology, American Heart Association, American College of Physicians-American Society of Internal Medicine Guidelines for the Management of Patients with Chronic Stable Angina: Treatment," *Annals of Internal Medicine*, Vol. 135, No. 8, 2001, pp. 616-632. [doi:10.7326/0003-4819-135-8_Part_1-200110160-00014](https://doi.org/10.7326/0003-4819-135-8_Part_1-200110160-00014)
- [17] M. Eccles, "North of England Stable Angina Guideline Development Group: North of England Evidence Based Guidelines Development Project: Summary Version of Evidence Based Guideline for the Primary Care Management of Angina," *BMJ*, Vol. 312, 1996, pp. 827-832. [doi:10.1136/bmj.312.7034.827](https://doi.org/10.1136/bmj.312.7034.827)
- [18] R. J. Gibbons, J. Abrams, K. Chatterjee, *et al.*, "ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina—Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina)," *Circulation*, Vol. 107, 2003, pp. 149-158. [doi:10.1161/01.CIR.0000047041.66447.29](https://doi.org/10.1161/01.CIR.0000047041.66447.29)
- [19] S. Silber, "Nitrates: Why and How Should They Be Used Today?" *European Journal of Clinical Pharmacology*, Vol. 3, No. 1, 1990, pp. S35-S51. [doi:10.1007/BF01417564](https://doi.org/10.1007/BF01417564)
- [20] P. A. Todd, K. L. Goa and H. D. Langtry, "Transdermal Nitroglycerin (Glyceryl Trinitrate): A Review of Its Pharmacology and Therapeutic Use," *Drugs*, Vol. 40, No. 6, 1990, pp. 880-902. [doi:10.2165/00003495-199040060-00009](https://doi.org/10.2165/00003495-199040060-00009)
- [21] S. Y. Zai, R. Chen and X. H. Wu, "Clinical Observation on Compound Salvia Pellet in the Treatment of 41 Cases' Migraine," *Journal of Practical, Traditional Chinese Medicine*, Vol. 22, No. 1, 2006, p. 26.
- [22] G. Y. Hu and F. H. Cai, "Clinical Observation of Curative Effect of Compound Danshen Pellet in Unstable Angina," *Chinese Journal of Cardiovascular Review*, Vol. 1, No. 1, 2003, pp. 38-40.