

Chinese herbal medicine *suxiao jiuxin wan* for angina pectoris (Review)

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ABSTRACT

Background

Suxiao jiuxin wan is widely used in China for angina pectoris.

Objectives

The objective of this review is to determine the effects (benefits and harms) of *suxiao jiuxin wan* in the treatment of angina pectoris.

Search strategy

We searched the Cochrane Central Register of Controlled Trials on *The Cochrane Library* (issue 4 2005), Medline (1995 to 2005), EMBASE (1995 to 2005), the Register of Chinese trials developed by the Chinese Cochrane Centre (to 2006), and the Chinese Biomedical Database (1995 to 2005), and handsearched 83 Chinese journals. We also searched reference lists, databases of ongoing trials and the Internet. Date of last search: November 2005.

Selection criteria

Randomised controlled trials of *suxiao jiuxin wan* compared to standard treatment in people with angina. Studies with a treatment duration > 4 weeks were included.

Data collection and analysis

Two reviewers independently applied the inclusion criteria, assessed trial quality and extracted the data.

Main results

Fifteen trials involving 1776 people were included. There was weak evidence that *suxiao jiuxin wan* compared with nitroglycerin (*xiaoxintong*) improved ECG measurements (RR 1.16, 95% CI 1.05 to 1.27), reduced symptoms (RR 1.09, 95% CI 1.04 to 1.13), reduced the frequency of acute attacks of angina (difference in means -0.70, 95% CI -0.90 to -0.50), reduced diastolic pressure (difference in means -3mmHg, 95% CI -5.73 to -0.27) and reduced the need for supplementary nitroglycerin (difference in means of -0.60, 95% CI -0.94 to -0.26). There was also weak evidence that *suxiao jiuxin wan* compared with *Salvia miltiorrhiza* (*danshen*) reduced symptoms (RR 1.21, 95% CI 1.11 to 1.31) and improved ECG measurements (RR 1.55, 95% CI 1.30 to 1.84). There was no significant difference when comparing *suxiao jiuxin wan* with isosorbide dinitrate (*xiaosuan'yishanlizhi*) both for ECG improvement (RR 1.34, 95% CI 0.91 to 1.98) and for symptom improvement (RR 1.11, 95% CI 0.86 to 1.43).

Authors' conclusions

Suxiao jiuxin wan appears to be effective in the treatment of angina pectoris and no serious side effects were identified. However, the evidence remains weak due to poor methodological quality of including studies.

PLAIN LANGUAGE SUMMARY

Angina pectoris is pain or discomfort within the chest, typically provoked by exertion or anxiety. Angina is a sign that someone is at increased risk of heart attack, cardiac arrest or sudden cardiac death. The aim of treatment for angina is to control the symptoms and

prevent a cardiovascular event such as a heart attack. In western medicine, treatment is usually with beta blockers, calcium channel blockers and nitrates (nitroglycerin). Suxiao jiuixin wan is widely used in China in conjunction with these western treatments. This review found weak evidence to suggest suxiao jiuixin wan alone or in combination with other anti-anginal drugs reduces the symptoms of angina. However, because of the quality of the research, the role of suxiao jiuixin wan is uncertain and more high quality trials are required to assess the effects of suxiao jiuixin wan in the long term.

BACKGROUND

Description of the condition

Ischaemic heart disease (IHD) is the most common cause of death in western countries, where it accounts for almost 33% of overall mortality (Braunwald 1992). In recent years, there has been a tendency for the incidence of IHD to increase in less developed countries as their economies develop. For instance in Beijing, China, the mortality from IHD rose from 21.7 per 100,000 in 1970 to 62.0 per 100,000 in 1980 (Chen 2000). The first clinical sign in over half of IHD patients is angina pectoris (Gibbons 1999). Angina pectoris is generally defined as pain or discomfort within (or adjacent to) the chest, which is typically provoked by exertion or anxiety. The pain usually lasts for several minutes and is alleviated by rest, and does not result in myocardial necrosis. Although angina may happen during exercise, strong emotions or extreme temperatures may result in some people, such as those with a coronary artery spasm, experiencing angina when they are resting. Angina is a sign that someone is at increased risk of heart attack, cardiac arrest or sudden cardiac death. The reported annual incidence of angina is 213 per 100,000 people over 30 years old in USA (Gibbons 1999).

About 30-40% of patients will have spontaneous remission of angina for 2 or more years (Cleland 1996). The most important determinants of prognosis are left ventricular systolic function, comorbid conditions, and the severity of coronary artery disease (Hilton 1991). In patients with good left ventricular function, despite severe coronary artery disease, the long-term prognosis is similar with medical treatment or surgical revascularisation procedures (Alderman 1990; Asirvatham 1998; Yusuf 1994).

Description of the intervention

Chinese herbal medicine is part of traditional Chinese medicine (TCM), which is a 3000-year-old holistic system of medicine combining the use of medicinal herbs, acupuncture, food therapy, massage, and therapeutic exercise for both treatment and prevention of disease (Fulder 1996). TCM has its unique theories for concepts of aetiology, systems of diagnosis and treatment that are vital to its practice. TCM drug treatment consists typically of complex prescriptions of a combination of several components. The combination, based on the Chinese diagnostic patterns (i.e. inspection, listening, smelling, inquiry, and palpation), follows a completely different rationale than many western drug treatments (Liu 2002).

In conventional medicine the purpose of treatment is to reduce angina attacks and to prevent cardiovascular events. Guidelines recommend that first-line drugs for angina are beta blockers. If these are not effective then nitrates to improve symptoms only, together with beta blockers to improve prognosis, are recommended. Patients who remain resistant to treatment are then treated with calcium-blockers, nitrates and beta-blockers (ACC/AHA 1999). However, there is an increased risk of bradycardia, heart block and additive negative inotropic effects with calcium and beta-blockers (Akhras 1991; Thadani 1999). Antianginal therapy with a single agent may be as effective as combination therapy with two or three agents (Jackson 2001). This has been demonstrated in two large randomized controlled trials (RCTs), TIBET (Fox 1996) and IM-AGE (Savonitto 1996). Clinical judgement is therefore essential when selecting optimal treatment plans for individual patients.

Suxiao jiuixin wan is a new drug on the national essential drug list of China for the treatment of cardiocerebral vascular diseases (Feng 2000). It has been shown to cause remission of angina pectoris (Yuan 2002), improve anginal symptoms, and reduce the use of nitroglycerin - a drug used to relieve quickly angina symptoms (Wei 1995). Suxiao jiuixin wan may be used on its own or in conjunction with conventional anti-anginal treatments. In China, some people who suffer from angina pectoris take suxiao jiuixin wan to prevent and treat angina pectoris. However, suxiao jiuixin wan can lead to gastrointestinal reactions in some cases, but these can be relieved by taking it after a meal (Han 2000).

How the intervention might work

In experimental studies, suxiao jiuixin wan was shown to significantly improve myocardial ischaemia and reduce the incidence of myocardial infarction by preventing hyperlipidaemia, improving microcirculation, increasing coronary arterial blood flow, dilating coronary vessels and improving myocardial blood supply (Liang 1999). The composition of suxiao jiuixin wan includes *Ligusticum chuanxiong Hort.* (also known as *Radix chuanxiong*) and *Borneolum syntheticum* (Zhuang 1999) (see Table 01 for further details of suxiao jiuixin wan composition). *Radix chuanxiong* dilates the coronary artery and increases the coronary flow. In aqueous solution or alcoholic infusion it can lower blood pressure. Its alkaloids, ferulic acid and cnidilide are antispasmodics. *Borneolum syntheticum* can increase the level of *Radix chuanxiong* in plasma (Liu 2003). Its solution, in low concentration, exerts anti-inflammatory, astringent and antiseptic effects. The side effects of *Borneolum syntheticum* are eye, skin and respiratory irritation. It may be harmful through

ingestion, inhalation or through skin contact (PTCL 2002).

Why it is important to do this review

The evidence on the effects of suxiao jiu xin wan has not been systematically assessed. The effects of this treatment need to be reviewed to inform clinical practice as well as highlight any areas for new research.

OBJECTIVES

The objective of this review is to determine the effects (benefits and harms) of suxiao jiu xin wan in the treatment of angina pectoris, in monotherapy or in combination with other antianginal therapy, as compared to placebo or other anti-anginal drugs.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled studies were included.

Types of participants

Participants were male or female of any age or ethnic origin with chronic angina pectoris. Participants with acute myocardial infarction, heart failure, hepatic failure and renal failure were excluded.

Types of intervention

We included any studies in which suxiao jiu xin wan was used for treating angina pectoris. We included studies where suxiao jiu xin wan was used alone versus other anti-anginal drugs (either western or traditional Chinese medicine) or placebo. We also accepted studies of suxiao jiu xin wan in combination therapy versus combination therapy without suxiao jiu xin wan. We excluded studies of less than 4 weeks treatment duration.

Types of outcome measures

Primary outcome measures

1. Mortality (sudden death from acute myocardial infarction)
2. Severity of angina pectoris
3. Frequency of acute attack angina
4. ECG improvement (an exercise ECG or a resting ECG)
5. Changes in dosage of nitroglycerin
6. Changes in symptoms (such as chest pain, breathlessness, etc)

Secondary outcome measures

1. Blood pressure
2. Levels of plasma endothelin level and nitric oxide
3. Health-related quality of life (ideally, using a validated instrument)
4. Adverse effects

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Heart Group methods used in reviews.

A comprehensive and exhaustive search strategy was formulated in an attempt to identify all relevant studies regardless of language or publication status.

Electronic searches

We searched The Cochrane Central Register of Controlled Trials (CENTRAL), on *The Cochrane Library* (issue 4, 2005) using the search term: 'suxiao jiu xin wan'.

The following electronic databases were also searched using the same term:

1. MEDLINE (1995 to 2005);
2. EMBASE (1995 to 2005);
3. CBM (Chinese biomedical database, 1995 to 2005);
4. Chinese Cochrane Centre Controlled Trials Register (to 2005).

We also searched databases of ongoing trials:

Current Controlled Trials (www.controlled-trials.com)

The National Research Register (www.update-software.com/National/nrr-frame.html)

Handsearches

We handsearched a number of Chinese traditional medicine journals. These are listed in Table 02. We attempted to identify additional studies by searching the reference lists of relevant trials and reviews identified. Authors of identified studies were contacted.

Other search strategies

Organisations (including the World Health Organisation), individual researchers working in the field, and medicinal herbs manufacturers (Tianjin Zhongxin Pharmaceuticals Co.Ltd.) were contacted in order to obtain possible additional references, unpublished trials, or ongoing trials, confidential reports and raw data of published trials.

METHODS OF THE REVIEW

Trial selection

The titles, abstracts and keywords of every record retrieved were scanned to determine which were possibly relevant to the review. Any record that appeared likely to meet the inclusion criteria was obtained in full text. If there was any doubt regarding eligibility from the information given in the title and abstract, the full article was retrieved for clarification. Differences in opinion between reviewers were resolved by discussion.

Quality assessment of trials

The quality of each trial was assessed based largely on the quality criteria specified by Schulz and by Jadad (Jadad 1996; Schulz 1995). In particular, the following factors were studied.

- Selection bias: a) was the randomization procedure adequate? b) was the allocation concealment adequate?
- Performance bias: were the patients and people administering the treatment blind to the intervention?
- Attrition bias: a) were withdrawals and dropouts completely described? b) was analysis by intention to treat?
- Detection bias: were outcome assessors blind to the intervention?

Based on these criteria, studies were broadly divided into the following three categories. This classification used as the basis of a sensitivity analysis. Additionally, we explored the influence of individual quality criteria in a sensitivity analysis.

- A: all quality criteria met - low risk of bias.
- B: one or more of the quality criteria only partly met - moderate risk of bias.
- C: one or more criteria not met - high risk of bias.

Each trial was assessed by two reviewers independently (XD, TW). Disagreements were resolved, where necessary, by recourse to a third reviewer (LZ). In cases of disagreement, the rest of the group were consulted and a judgement was made based on consensus.

Data extraction

Data concerning details of study population, intervention and outcomes were extracted independently by two reviewers (XD, TW). Differences in data extraction were resolved by consensus, referring back to the original article. When necessary, information was sought from the authors of the primary studies. Disagreement were resolved by discussion and, where necessary, in consultation with a third reviewer (LZ). For binary outcomes, number of events and total number in each group were extracted. For continuous outcomes, mean, standard deviation and sample size of each group were abstracted or imputed.

The data extraction form included the following items:

1. General information: published/unpublished, title, authors, reference/source, contact address, country, urban/rural etc., language of publication, year of publication, duplicate publications, sponsor, and setting.
2. Trial characteristics: design, duration of follow-up, method of randomisation, allocation concealment, blinding (patients, people administering treatment, outcome assessors).
3. Intervention(s): intervention(s) (dose, route, and timing), comparison intervention(s) (dose, route, and timing), and co-medication (dose, route, and timing).
4. Patients: exclusion criteria, total number and number in comparison groups, age (adults), baseline characteristics, diagnostic criteria, similarity of groups at baseline (including any co-morbidity), assessment of compliance, withdrawals/losses to follow-up (reasons/description), subgroups.

5. Outcomes: outcomes specified above, any other outcomes assessed, other events, length of follow-up, quality of reporting of outcomes.

6. Results: for outcomes and times of assessment (including a measure of variation), if necessary converted to measures of effect specified below, intention-to-treat analysis.

Subgroup analyses

We planned to perform subgroup analyses in order to explore effect size differences as follows:

1. Duration of treatment (4 weeks versus > 4 weeks); and
2. Patients with Asian ethnic origin compared with non-Asians.

Sensitivity analyses

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

1. Repeating the analysis excluding unpublished studies; and
2. Repeating the analysis taking account of study quality, as specified above.

Heterogeneity between trials results was tested using a standard chi-squared test. The results are reported as risk ratios (RR) with corresponding 95% confidence interval (CI) for dichotomous data using the fixed-effect model (APT 1994). For continuous data, the difference in means are computed for outcomes measured on the same scale.

DESCRIPTION OF STUDIES

A total of 54 studies of *suxiao jiu xin wan* for angina pectoris were identified by the searches. All were published in Chinese. No unpublished studies or other information was obtained from contact with WHO, individual researchers and herb manufactures. Of the 54 studies, 39 were excluded upon further scrutiny. Details of the excluded studies are shown in the characteristics of excluded studies. Studies excluded for not being randomised controlled trials (Cheng 2005; Feng 2000; Gao 2003; Han 2000; Hu 2000c; Jia 2000; Lai 2003; Li 1996; Li 1998; Li 1999; Li 2000b; Li 2000c; Liang 1995; Liu 1996a; Liu 1996b; Liu 1996c; Lu 2000; Luo 2002; Pu 2000; Wang 1996; Wang 2000b; Wang 2000c; Wei 1995; Yuan 2000; Yuan 2002; Zhang 1997; Zhang 2000b; Zhou 2000a; Zhou 2000b; Zhou 2002; Zhu 2005; Zhuang 1999), not reporting relevant outcomes (Duan 2002; Ma 2004; Wu 2003), other drugs potentially interfering with the outcomes (Cai 2003; Zheng 2003) and study duration < 4 weeks (Guo 1996; Hou 2000).

Included studies

Details of the 15 included studies are shown in the characteristics of included studies table. All studies included were of a parallel design, single centre and had a positive control group. For the randomisation procedure units for allocation were all individuals. Trial duration ranged from 4 weeks to 2 years. Trials came only

from China and were written in Chinese. Numbers of participants of the individual studies ranged from 48 to 248 with a total of 1776 participants included in this review. Ages of participants ranged from 35 to 85 years old. 664 participants were women.

Interventions in included studies

Eleven of the studies used nitroglycerin (also known as xiaoxintong) in the control group (Gao 1996; Hu 2000a; Hu 2000b; Ji 1996; Li 2000a; Liu 2000; Shi 2002; Sun 2002; Tang 2000; Yang 2000; Zhang 2000a). In three studies, *Salvia miltiorrhiza* (also known as danshen) was used as the control (He 1995; Song 1995; Wang 2000a). Pharmacological studies have shown that danshen can reduce blood viscosity, dilate blood vessels, reduce arterial pressure, improve platelet function, anticoagulate, stabilise cell membrane, maintain cell function and fight infection (Cai 1999). In one study isosorbide dinitrate (Xiaosuanyishanlizhi) was the control (Zhan 2000). Only two studies lasted longer than 4 weeks (Gao 1996; Liu 2000), the remaining 13 studies had a duration of 4 weeks (He 1995; Hu 2000a; Hu 2000b; Ji 1996; Li 2000a; Shi 2002; Song 1995; Sun 2002; Tang 2000; Wang 2000a; Yang 2000; Zhan 2000; Zhang 2000a). All interventions were given orally. The treatment regimen of suxiao jiu xin wan varied in the studies: four pills were used in two studies (He 1995; Song 1995); five pills in eight studies (Li 2000a; Liu 2000; Sun 2002; Shi 2002; Tang 2000; Wang 2000a; Zhan 2000; Zhang 2000a); four to six pills in one study (Hu 2000a); six pills in two studies (Hu 2000b; Ji 1996) and 10 pills in two studies (Gao 1996; Yang 2000). In two studies participants in both groups were given additional treatments (Hu 2000a; Wang 2000a).

Outcome measures in included studies

None of the studies assessed mortality, severity of angina pectoris, levels of plasma endothelin level and nitric oxide or health-related quality of life. One study (Hu 2000b) reported frequency of acute attacks of angina. All studies reported on 'symptom improvement'. Thirteen studies (Gao 1996; Hu 2000a; Hu 2000b; Ji 1996; Li 2000a; Liu 2000; Shi 2002; Song 1995; Sun 2002; Tang 2000; Yang 2000; Wang 2000a; Zhang 2000a) reported on ECG improvement. One study (Hu 2000a) reported on the frequency of taking nitroglycerin. One study (Tang 2000) reported changes in blood pressure.

METHODOLOGICAL QUALITY

All studies were of poor methodological quality, and are at high risk of bias. All studies were described as 'randomised' but none of the studies mentioned allocation concealment. No study mentioned blinding of participants or of outcome assessors. None of the studies provided any data on dropouts. In all studies the characteristics of participants in different treatment groups were similar at baseline (age, sex, race, severity of angina and smoking status).

RESULTS

Most of the 15 included trials did not separately report on all 10 outcome measures of interest. Data were only available for the following outcomes: symptom improvement (15 trials), frequency of acute attacks (one trial), changes in blood pressure (one trial) and ECG improvement (13 trials).

Suxiao jiu xin wan compared to nitroglycerin (xiaoxintong)

There was evidence from one trial that suxiao jiu xin wan reduced frequency of acute angina attacks compared to nitroglycerin use (difference in means -0.70, 95% CI -0.50 to -0.90, $P < 0.00001$). In the one trial with relevant data, there was evidence of a small fall in diastolic blood pressure (difference in means -3mmHg, 95% CI -5.73 to -0.27) but no difference in systolic blood pressure (difference in means 0.7mmHg, 95% CI -3.13 to 4.53). Patients in 10 studies taking suxiao jiu xin wan had better ECG results than those taking nitroglycerin (RR 1.16, 95% CI 1.05 to 1.27, $P = 0.0003$). In 10 trials, patients on suxiao jiu xin wan reported better symptom improvement compared to those on nitroglycerin (RR 1.09, 95% CI 1.04 to 1.13, $P = 0.0003$). There was evidence from one trial that people receiving suxiao jiu xin wan took fewer supplementary nitroglycerin doses than those receiving nitroglycerin only (difference in means -0.60, 95% CI -0.94 to -0.26, $P = 0.0005$).

Suxiao jiu xin wan compared to *Salvia miltiorrhiza* (danshen)

Two studies reported improvement in ECG for people taking suxiao jiu xin wan as compared to those taking *Salvia miltiorrhiza* (danshen) (RR 1.55, 95% CI 1.30 to 1.84, $P < 0.0001$) There was no evidence of heterogeneity ($\chi^2 = 0.19$, $df = 1$, $P = 0.67$, $I^2 = 0\%$). Patients receiving suxiao jiu xin wan reported more symptom improvement compared to those receiving danshen (RR 1.21, 95% CI 1.11 to 1.31, $P < 0.0001$). There was no evidence of heterogeneity ($\chi^2 = 0.80$, $df = 2$, $P = 0.67$, $I^2 = 0\%$).

Suxiao jiu xin wan compared to isosorbide dinitrate (xiaosuanyishanlizhi)

In one study, there was no evidence to show suxiao jiu xin wan improved ECG compared to isosorbide dinitrate (RR 1.34, 95% CI 0.91 to 1.98) and no evidence to show suxiao jiu xin wan improved symptoms (RR 1.11, 95% CI 0.86 to 1.43).

Subgroup analyses

The trend toward greater ECG improvement in the suxiao jiu xin wan group compared to nitroglycerin group with duration of treatment of 4 weeks (RR 1.13, 95% CI 1.02 to 1.25) was similar to studies with a treatment duration of more than 4 weeks (RR 1.27, 95% CI 0.99 to 1.62).

There was only very weak evidence of any improvement in symptoms in the suxiao jiu xin wan group compared to the nitroglycerin group with a treatment duration of 4 weeks (RR 1.07, 95% CI 1.02 to 1.13). In those treated for longer than 4 weeks the evidence favoured treatment with suxiao jiu xin wan but there was

significant heterogeneity (RR 1.13, 95% CI 1.03 to 1.23, $\chi^2 = 4.20$, $df = 1$, $P = 0.04$, $I^2 = 76.2\%$).

Sensitivity analyses

We did not carry out any of the planned sensitivity analyses as no unpublished studies were found and all included studies were of poor methodological quality (graded C - high risk of bias).

DISCUSSION

We found a tendency towards symptom improvement with *suxiao jiu xin wan*. However, all identified studies were of poor quality and many of the outcome measures that we considered to be important were not assessed. There was a lack of clinically relevant event outcomes and no measure of patient quality of life. In the studies identified, differing treatment regimes were used and outcomes were measured in different ways.

Limitations of the review

The conclusions of this review must be considered with great caution. Only a small number of studies were included in this review, and none of these abided by the criteria laid down in the CONSORT statement (CONSORT 2001). The reporting of quality issues in the studies was generally poor. For most of the trials the method of randomisation was not reported clearly, and none of the trials reported blinding of assessors of outcomes. The poor evidence does not allow any conclusion regarding the effectiveness of *suxiao jiu xin wan* per se and none of the included studies were ideally suited to investigate the effectiveness of *suxiao jiu xin wan* in treating angina pectoris. While *suxiao jiu xin wan* is undoubtedly the most widely used treatment for angina pectoris in China, the results of the review suggest that it is not suitable for all situations. We intend to look at this in a future review.

The review included studies only conducted in China. Delivery of treatment and quality control of *suxiao jiu xin wan* is probably a little difficult in remote areas in China and this method of treating angina pectoris may therefore be problematic.

Studies generally concentrated on measuring angina improvement by ECG - presumably because these measurements can be easily and quickly obtained. However, these values may not reflect long-term clinical improvement and therefore other indicators should be used, for example, the need for additional nitroglycerin to control symptoms of an attack, frequency of acute angina attacks, levels of plasma endothelin level and nitric oxide or health-related quality of life. These would give a more accurate picture of any improvement.

There have been concerns about adverse effects of *suxiao jiu xin wan*. Abdomen discomfort (Ji 1996; Liu 2000), thirst (Song 1995) and reddening of the skin (Ji 1996; Song 1995; Tang 2000) were reported. These symptoms were not serious and could be tolerated by patients. Headache was reported in some of the included

studies (Ji 1996; Song 1995; Tang 2000; Zhang 2000a), as was bradycardia (Zhang 2000a). However symptoms of bradycardia and headache were not often severe; symptoms were relieved after a short rest and none of the patients who had these symptoms needed special management.

AUTHORS' CONCLUSIONS

Implications for practice

Although trials of *suxiao jiu xin wan* alone or in combination with other anti-anginal treatments showed weak evidence of a reduction in symptoms and an improvement in ECG measurements, methodological concerns including concealment of allocation, lack of blinding, lack of statistical power, lack of information on hazards of treatment, and lack of other clinically relevant outcomes, make the role of *suxiao jiu xin wan* in the management of angina pectoris uncertain.

Implications for research

More high quality controlled trials are required for assessing the effects of *suxiao jiu xin wan* in comparison to other drugs. These studies should also address the most effective dosage to be used (under given conditions). Studies should be large and long term, lasting at least 1 year, including participants of all ages. The outcomes studied should not be restricted to symptom improvement and ECG improvement, but should include the other outcome measures specified above, such as mortality and health-related quality of life. Special attention should be paid to adverse effects and methodological challenges, such as inadequate randomisation, blinding, sample size, need to be tackled.

POTENTIAL CONFLICT OF INTEREST

None known.

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TABLES**Characteristics of included studies**

Study	Gao 1996
Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 2 years and 4 months Location: China Hebei
Participants	147 people (35-85 years) 82 men and 65 women
Interventions	1. Suxiao jiu xin wan (10 pills when angina attack) n = 105 2. Nitroglycerin (0.5mg when angina attack) n = 42
Outcomes	Symptoms improvement, ECG, adverse effects
Notes	
Allocation concealment	D – Not used

Study	He 1995
Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Jiangsu
Participants	48 people (40-60 years) 33 men and 15 women
Interventions	1. Suxiao jiu xin wan (4 pills three times a day and 10 pills when angina attack) n = 26 2. Dansheng pill (3 pills three times a day and 0.5 mg nitroglycerin when angina attack) n = 22
Outcomes	Symptoms improvement, haemodynamics, adverse effects
Notes	
Allocation concealment	D – Not used

Study	Hu 2000a
Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Anhui
Participants	112 people (41-76 years) 73 men and 39 women
Interventions	Other treatment: aspirin 75 mg three times a day, vit.C 200mg once a day, vit.E 100mg three times a day, fufang danshengpian 3 pills three times a day. 1. Suxiao jiu xin wan (4-6 pills three times a day and 10-15 pills when angina attack) n = 56

Characteristics of included studies (Continued)

	2. Xiaoxintong (10 mg) n = 56
Outcomes	Symptoms improvement, ECG, adverse effects
Notes	
Allocation concealment	D – Not used

Study	Hu 2000b
Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Tianjin
Participants	128 people(43-75 years) 78 men and 50 women
Interventions	1. Suxiao jiuxin wan (6 pills, three times a day and 10 pills when angina attack) n = 68 2. Xinxiaotong (10 mg) n = 60
Outcomes	Symptoms improvement, ECG, adverse effects
Notes	
Allocation concealment	D – Not used

Study	Ji 1996
Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Guizhou
Participants	72 people(45-79 years) 43 men and 39 women
Interventions	1. Suxiao jiuxin wan (6 pills three times a day and 10 pills when angina attack) n = 36 2. Nitroglycerin (0.5mg three times a day and 0.5 mg when angina attack) n = 36
Outcomes	Symptoms improvement, ECG, adverse effects
Notes	
Allocation concealment	D – Not used

Study	Li 2000a
Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Anhui
Participants	56 people(49-65 years) 37 men and 19 women
Interventions	1. Suxiao jiuxin wan (5 pills and nitroglycerin 0.5 mg when angina attack) n = 30 2. Xiaoxintong (10 mg) n = 26
Outcomes	Symptoms improvement, ECG, adverse effects
Notes	
Allocation concealment	D – Not used

Study	Liu 2000
Methods	Randomised controlled trial, not blinded

Characteristics of included studies (Continued)

	Comparison: individuals Duration: 60 days Location: China, Jiangxi
Participants	138 people(46-72 years) 92 men and 46 women
Interventions	1. Suxiao jiu xin wan (5 pills three times a day) n = 78 2. Xiaoxintong (10 mg three times a day) n = 60
Outcomes	Symptoms improvement, ECG, adverse effects
Notes	
Allocation concealment	D – Not used

Study Shi 2002

Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Shanghai
Participants	70 people(50-65 years) 37 men and 35 women
Interventions	1. Suxiao jiu xin wan(5 pills three times a day) n = 40 2. Xiaoxintong (10 mg three times a day) n = 30
Outcomes	ECG improvement, symptoms improvement
Notes	
Allocation concealment	D – Not used

Study Song 1995

Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Shandong
Participants	184 people 133 men and 51 women(45-74 years)
Interventions	1. Suxiao jiu xin wan (5 pills three times a day and 10-15 pills when angina attack) n = 102 2. Dansheng pills (3 pills three times a day) n = 82
Outcomes	Frequency of acute attack angina, ECG improvement, BP and HR, symptoms improvement, adverse effects
Notes	
Allocation concealment	D – Not used

Study Sun 2002

Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Shandong
Participants	100 people (37-72 years) 62 men and 38 women
Interventions	1. Suxiao jiu xin wan (5 pills three times a day and 10-15 pills when angina attack) n = 50 2. Xiaoxintong (10 mg threes a day and 10-20 mg when angina attack) n = 50

Characteristics of included studies (Continued)

Outcomes	Symptoms improvement, ECG improvement
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Notes	
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Allocation concealment	D – Not used
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Study Tang 2000

Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Hubei
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Participants	248 people (46-78 years) 138 men and 110 women
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Interventions	1. Suxiao jiu xin wan (5 pills three times a day and 10 pills when angina attack) n = 124 2. Xiaoxintong (10 mg threes a day and 10 mg when angina attact) n = 124
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Outcomes	Symptoms improvement, ECG improvement, HR, BP and RPP, adverse effects
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Notes	
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Allocation concealment	D – Not used
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Study Wang 2000a

Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, LiaoYang
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Participants	232 people (41-79 years) 154 men and 78 women
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Interventions	Other treatment: isoine 0.2g, threes a day; vit B1,10 mg, three times a day 1. Suxiao jiu xin wan (4 pills three times a day) n = 128 2. Dansheng pills (3 pills three times a day) n = 104
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Outcomes	Symptoms improvement , ECG improvement, adverse effects
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Notes	
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Allocation concealment	D – Not used
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Study Yang 2000

Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Shandong
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Participants	86 people (38-69 years) 56 men and 30 women
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Interventions	1. Suxiao jiu xin wan (10 pills three times a day) n = 46 2. Xiaoxintong (10 mg three times a day) n = 40
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Outcomes	Symptoms improvement, ECG improvement, adverse effects
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Notes	
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Allocation concealment	D – Not used
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Study Zhan 2000

Methods	Randomised controlled trial, not blinded
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	Comparison: individuals Duration: 4 weeks Location: China, Hubei
Participants	60 people (43-69 years) 48 men and 12 women
Interventions	1. Suxiao jiuxin wan (5 pills three times a day) n = 31 2. Xiaoshuanyishanlizhi (isosorbide dinitrate) (10 mg three times a day) n = 29
Outcomes	Symptoms improvement, ECG improvement, adverse effects
Notes	
Allocation concealment	D – Not used

Study	Zhang 2000a
Methods	Randomised controlled trial, not blinded Comparison: individuals Duration: 4 weeks Location: China, Hubei
Participants	91 people (46-64 years) 54 men and 37 women
Interventions	1. Suxiao jiuxin wan (5 pills three times a day and 10-15 pills when angina attack) n = 30 2. Xiaoxintong (10-15mg three times a day) n = 28
Outcomes	Symptoms improvement, adverse effects
Notes	
Allocation concealment	D – Not used

Characteristics of excluded studies

Study	Reason for exclusion
Cai 2003	Interfered by other drugs (aspirin) only control group used
Cheng 2005	Not a randomised controlled trial
Duan 2002	Did not present outcomes of interest (ejection fraction, cardiac output, cardiac minute output and haematodynamics)
Feng 2000	Not a randomised controlled trial
Gao 2003	Not a randomised controlled trial
Guo 1996	Insufficient duration (only 2 weeks)
Han 2000	Not a randomised controlled trial
Hou 2000	Insufficient duration (only 10 days)
Hu 2000c	Not a randomised controlled trial
Jia 2000	Not a randomised controlled trial
Lai 2003	Not a randomised controlled trial
Li 1996	Not a randomised controlled trial
Li 1998	Not a randomised controlled trial
Li 1999	Not a randomised controlled trial
Li 2000b	Not a randomised controlled trial
Li 2000c	Not a randomised controlled trial
Liang 1995	Not a randomised controlled trial
Liu 1996a	Not a randomised controlled trial

Characteristics of excluded studies (Continued)

Liu 1996b	Not a randomised controlled trial
Liu 1996c	Not a randomised controlled trial
Lu 2000	Not a randomised controlled trial
Luo 2002	Not a randomised controlled trial
Ma 2004	have not the result that we wanted
Pu 2000	Not a randomised controlled trial
Wang 1996	Not a randomised controlled trial
Wang 2000b	Not a randomised controlled trial
Wang 2000c	Not a randomised controlled trial
Wei 1995	Not a randomised controlled trial
Wu 2003	have not the result that we wanted
Yuan 2000	Not a randomised controlled trial
Yuan 2002	Not a randomised controlled trial
Zhang 1997	Not a randomised controlled trial
Zhang 2000b	Not a randomised controlled trial
Zheng 2003	Interfered by other drugs (drugs for diabetes and hypertension, the study didn't report the name of the drugs)
Zhou 2000a	Not a randomised controlled trial
Zhou 2000b	Not a randomised controlled trial
Zhou 2002	Not a randomised controlled trial
Zhu 2005	Not a randomised controlled trial
Zhuang 1999	Not a randomised controlled trial

ADDITIONAL TABLES

Table 01. Composition of suxiao jiuxin wan

Common name	Latin name	Alternative name
chuanxiong	Ligusticum chuanxiong Hort.	Radix chuanxiong
bingpian	Borneolum syntheticum	Borneol

Table 02. Handsearched traditional Chinese medicine journals

Journals

Acta Chinese Medicine and Pharmacology
Beijing Journal of Medicine
Beijing Journal of Traditional Chinese Medicine
China Journal of Chinese Materia Medica
China Journal of Basic Medicine in Traditional Chinese Medicine
Chinese Journal of Integrated Traditional and Western Medicine
Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care
Chinese Journal of Traditional Medical Science and Technology
Chinese Journal of Traditional & Western Medicine

Table 02. Handsearched traditional Chinese medicine journals (Continued)

Journals

Chinese Medicine
Chinese Traditional Patent Medicine
Chinese Traditional Patent Medicine Research
Chinese Traditional and Herbal Drags
Chinese Pharmaceutical Abstracts
Clinical Journal of Anhui Traditional Chinese Medicine
Critical Care
Forum on Traditional Chinese Medicine
Fujian Journal of Medicine
Fujian Journal of Traditional Chinese Medicine
Guang Ming Zhong Yi Journal of Traditional Chinese Medicine
Gansu Journal of Medicine
Gansu Journal of Traditional Chinese Medicine
Guangxi Journal of Medicine
Guangxi Journal of Traditional Chinese Medicine
Gangdong Journal of Medicine
Guangdong Journal of Traditional Chinese Medicine
Hebei Integrated Traditional and Western Medicine
Hebei Journal of Medicine
Hebei Journal of Traditional Chinese Medicine
Heilongjiang Journal of Medicine
Heilongjiang Journal of Traditional Chinese Medicine
Henan Journal of Medicine
Henan Journal of Traditional Chinese Medicine and Pharmacy
Henan Journal of Traditional Chinese Medicine
Hubei Journal of Traditional Chinese Medicine
Hunan Journal of Medicine
Hunan Journal of Traditional Chinese Medicine
Information on Traditional Chinese Medicine
Jiangxi Journal of Medicine
Jiangxi Journal of Traditional Chinese Medicine
Jiangsu Journal of Medicine
Jiangshu Journal of Traditional Chinese Medicine
Jilin Journal of Medicine
Jilin Journal of Traditional Chinese Medicine
Journal of Anhui College of Traditional Chinese Medicine
Journal of Beijing University of Traditional Chinese Medicine
Journal of Chengdu University of Traditional Chinese Medicine
Journal of Chinese Medicinal Materials
Journal of Emergency in Traditional Chinese Medicine
Journal of Guangzhou University of Traditional Chinese Medicine
Journal of HeNnan College of Traditional Chinese Medicine
Journal of Integrated Traditional and Western Medicine
Journal of Practical Traditional Chinese Medicine
Journal of Practical Chinese Traditional Internal Medicine
Journal of Sichuan of Traditional Chinese Medicine
Journal of Sichuan Medicine
Journal of Traditional Chinese Medicine
Journal of Emergency Syndromes in Chinese Medicine

Table 02. Handsearched traditional Chinese medicine journals (Continued)

Journals

Liaoning Journal of Traditional Chinese Medicine
 Modern Journal of Integrated Chinese Traditional and Western Medicine
 Modern Traditional Chinese Medicine
 Neimongol Journal of Traditional Chinese Medicine
 New Journal of Traditional Chinese Medicine
 Pharmacology and Clinics of Chinese Materia Medica
 Research of Traditional Chinese Medicine
 Sanxi Journal of Medicine
 Shanxi Journal of Traditional Chinese Medicine
 Shanxi Journal of Medicine
 Shanxi Journal of Traditional Chinese Medicine
 Shandong Journal of Medicine
 Shandong Journal of Traditional Chinese Medicine
 Shanghai Journal of Medicine
 Shanghai Journal of Traditional Chinese Medicine
 Shenzhen Journal of Integrated Traditional and Western Medicine
 Tianjin Journal of Medicine
 Tianjin Journal of Traditional Chinese Medicine
 Traditional Chinese Medicine Research
 Xinjiang Journal of Medecine
 Xinjiang Journal of Traditional Chinese Medicine
 Yunnan Journal of Medicine
 Yunnan Journal of Traditional Chinese Medicine
 Yunnan Journal of Traditional Chinese Medicine and Materia Medica
 Zhejiang Journal of Traditional Chinese Medicine

A N A L Y S E S

Comparison 01. Suxiao jiuxin wan vs nitroglycerin (xiaoxintong)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 ECG improvement	10	1147	Relative Risk (Fixed) 95% CI	1.16 [1.05, 1.27]
02 Frequency of acute attacks of angina			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
03 Frequency of nitroglycerin use			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
04 Symptom improvement	11	1252	Relative Risk (Fixed) 95% CI	1.09 [1.04, 1.13]
05 Blood pressure			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 02. Suxiao jiuxin wan vs salvia miltiorrhiza (danshen)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 ECG improvement			Relative Risk (Fixed) 95% CI	Subtotals only
02 Symptom improvement			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 03. Suxiao jiuxin wan vs isosorbide dinitrate (xiaosuanyishanlizhi)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 ECG improvement			Relative Risk (Fixed) 95% CI	Totals not selected
02 Symptom improvement			Relative Risk (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Angina Pectoris [*drug therapy]; Drugs, Chinese Herbal [*therapeutic use]; Isosorbide Dinitrate [therapeutic use]; Nitroglycerin [therapeutic use]; *Phytotherapy; Randomized Controlled Trials as Topic; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans

COVER SHEET

Title	Chinese herbal medicine suxiao jiuxin wan for angina pectoris
Authors	Duan X, Zhou L, Wu T, Liu G, Qiao J, Wei J, Ni J, Zheng J, Chen X, Wang Q
Contribution of author(s)	Xin Duan, Taixiang Wu, Likun Zhou: conceived the review, prepared and designed the protocol, coordinated the review process, developed and ran search strategy, screened results, organised retrieval of papers, extracted data, helped interpret data and provided a methodological, policy and clinical perspective on the data, participated in writing the review. Guanjian Liu: appraised papers, extracted and analysed data. Jieqi Qiao, Qin Wang, Liu Chang, Jiafu Wei, Juan Ni, Jie Zheng, Xiaoyan Chen: searched for trials.
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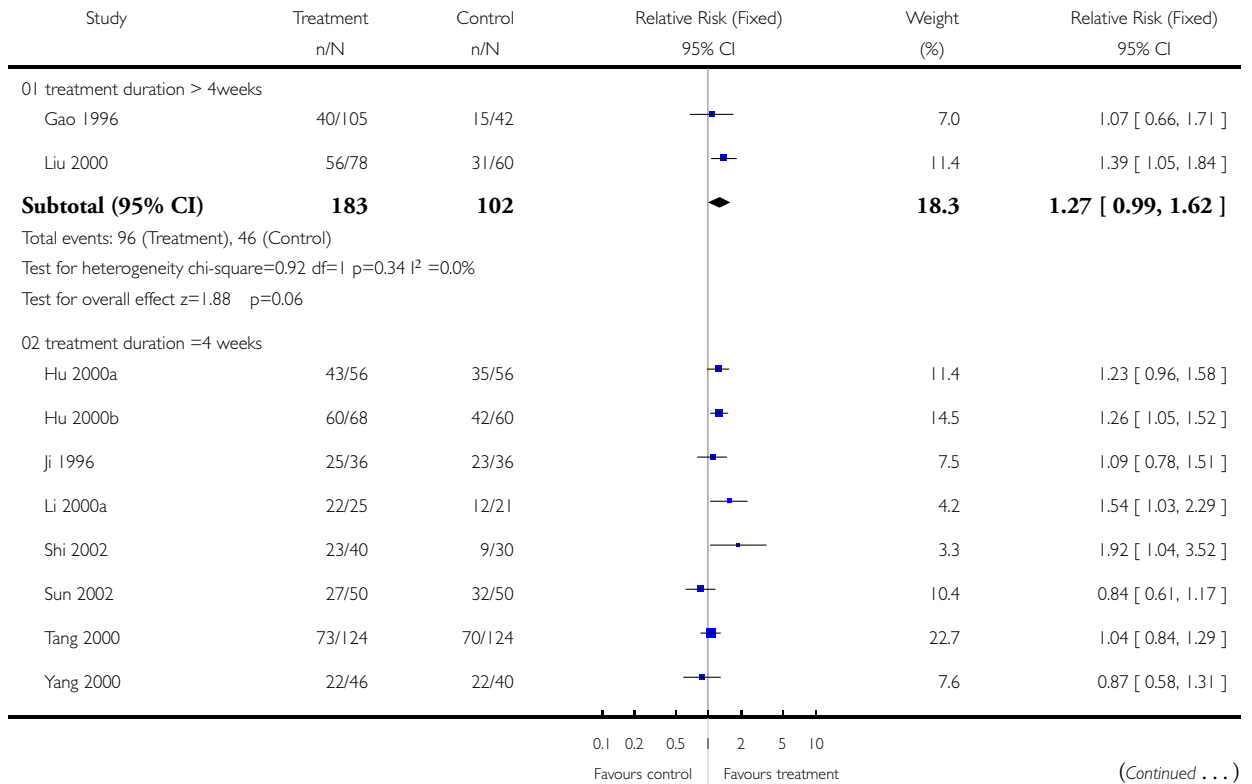
GRAPHS AND OTHER TABLES

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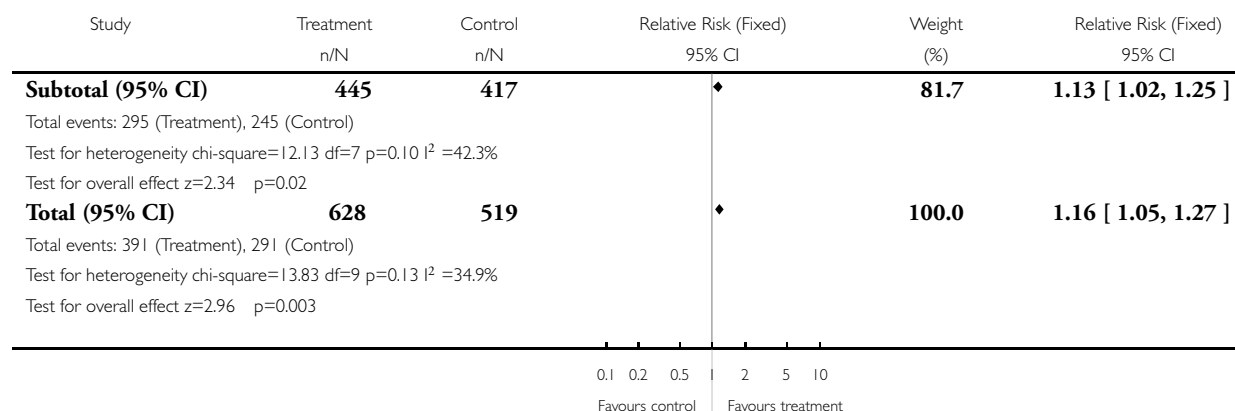
Review: Chinese herbal medicine suxiao jiuixin wan for angina pectoris

Comparison: 01 Suxiao jiuixin wan vs nitroglycerin (xiaoxintong)

Outcome: 01 ECG improvement



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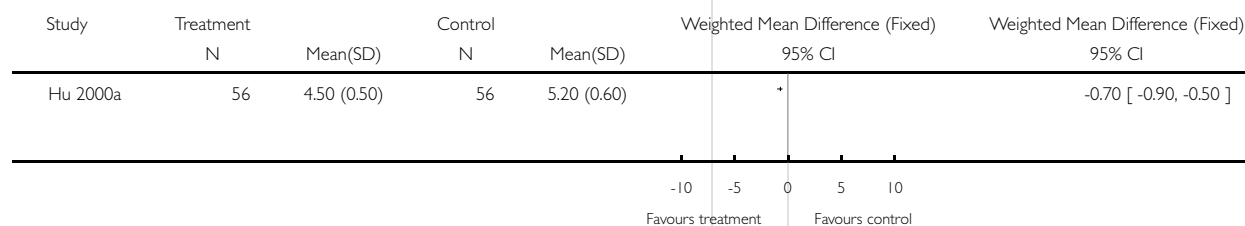


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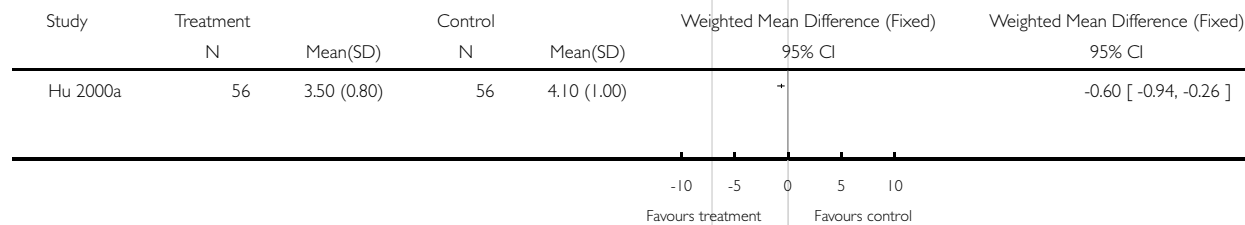


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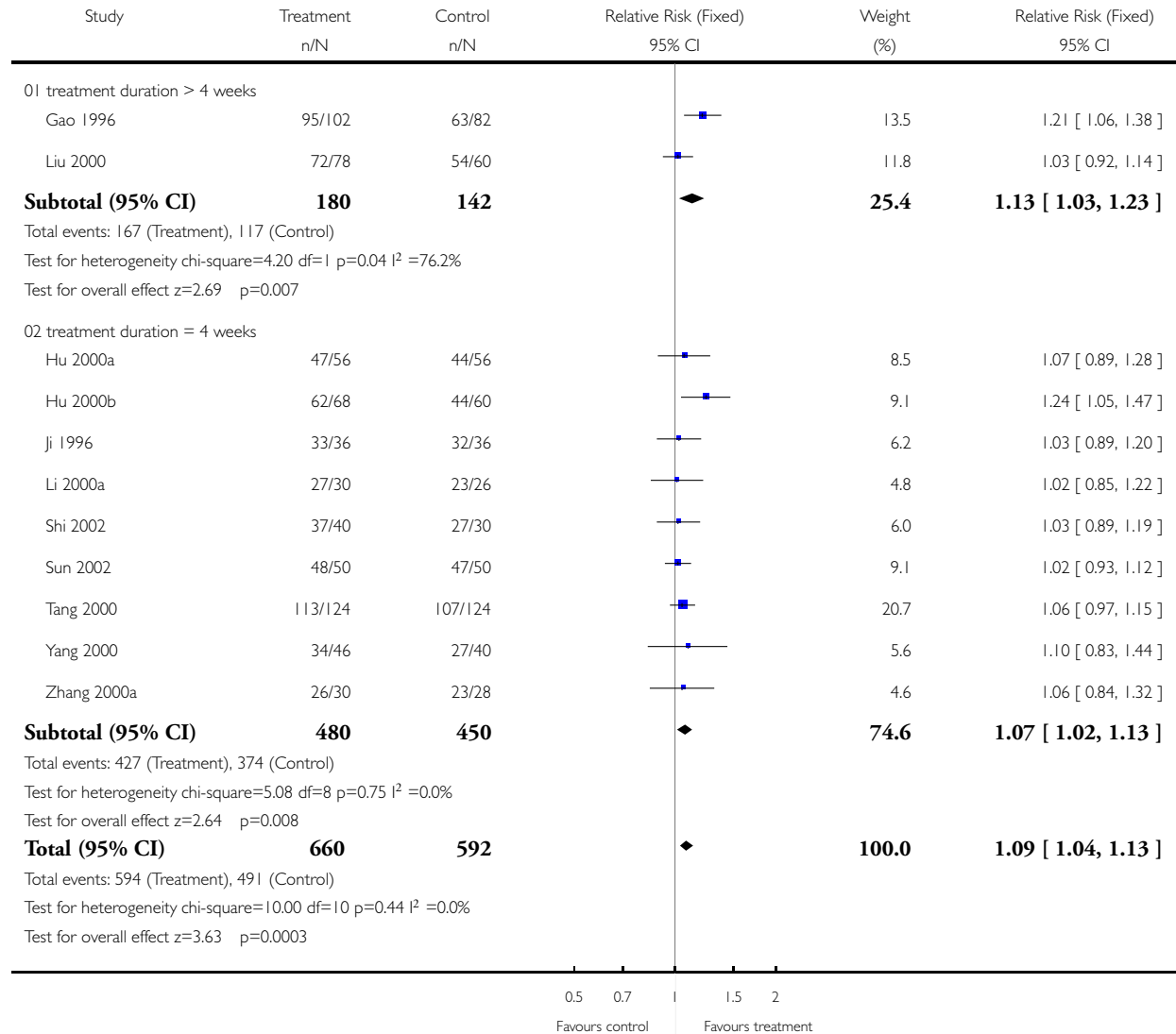


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Review: Chinese herbal medicine suxiao jiuixin wan for angina pectoris

Comparison: 01 Suxiao jiuixin wan vs nitroglycerin (xiaoxintong)

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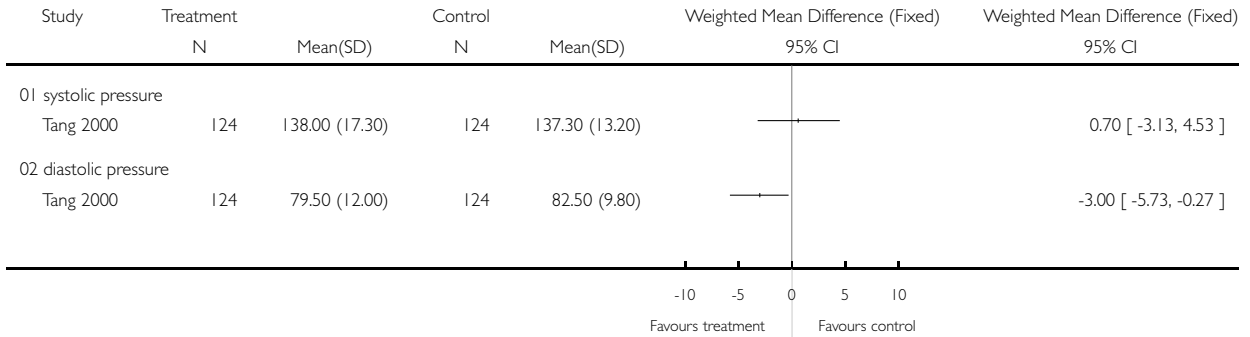


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Review: Chinese herbal medicine suxiao jiu xin wan for angina pectoris

Comparison: 01 Suxiao jiu xin wan vs nitroglycerin (xiaoxintong)

Outcome: 05 Blood pressure

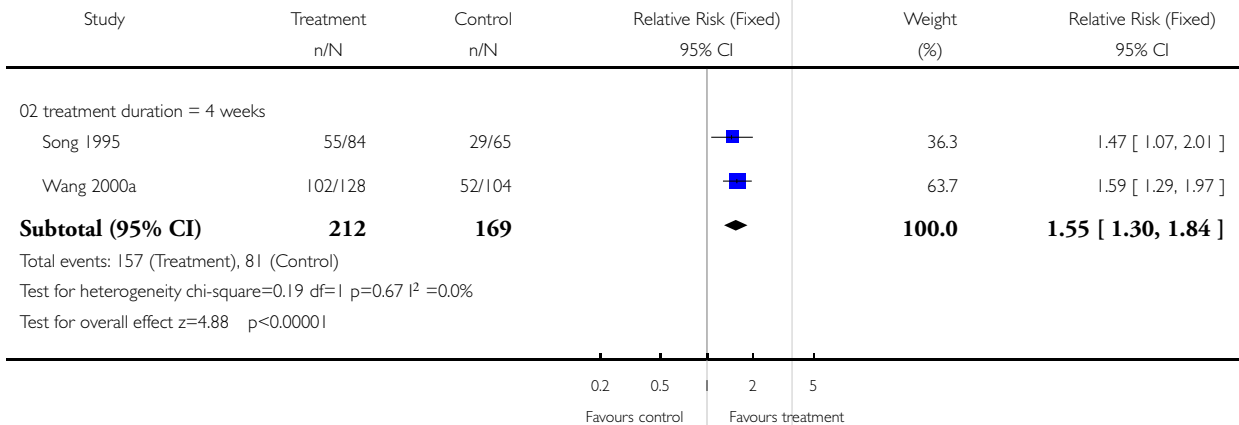


Analysis 02.01. Comparison 02 Suxiao jiu xin wan vs salvia miltiorrhiza (danshen), Outcome 01 ECG improvement

Review: Chinese herbal medicine suxiao jiu xin wan for angina pectoris

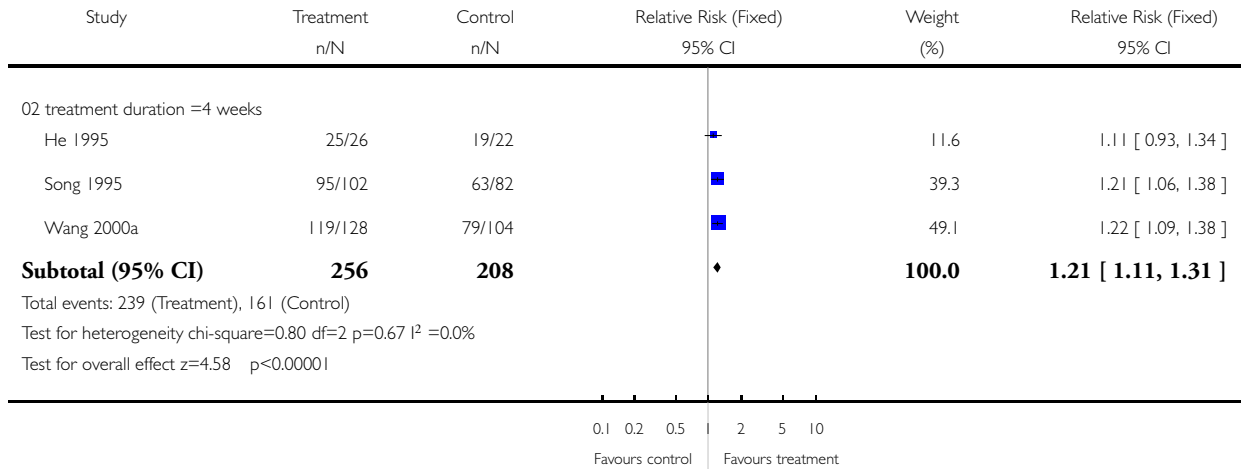
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Outcome: 01 ECG improvement



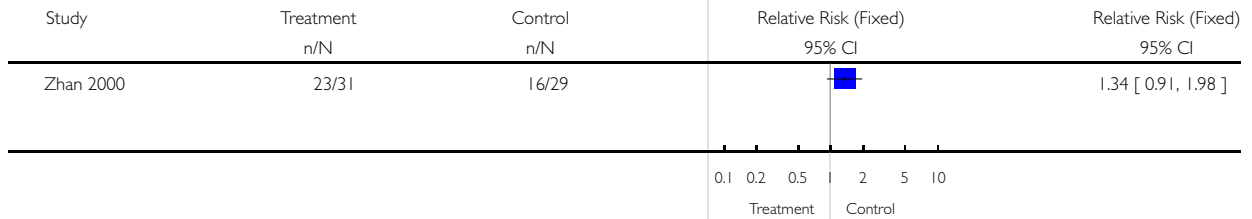
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Analysis 03.02. Comparison 03 Suxiao jiu xin wan vs isosorbide dinitrate (xiaosuanyishanlizhi), Outcome 02 Symptom improvement

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Outcome: 02 Symptom improvement

