Clinical epidemiology survey of the traditional Chinese medicine etiology and syndrome differentiation of coronary artery disease: study protocol of a multicenter trial

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BACKGROUND: Coronary artery disease (CAD), a common disease with high incidence and mortality rate, has seriously threatened the health and life of the public. Traditional Chinese medicine (TCM) has an important role in the prevention and treatment of this disease. Through clinical epidemiological survey, a deeper understanding of TCM etiology and syndrome characteristics in CAD would further improve clinical efficacy in the treatment of this disease.

METHODS/DESIGN: The preliminary clinical questionnaire for TCM etiology and syndrome differentiation in CAD was designed after literature reviews and analysis. Through a series of clinical pre-surveys, expert consultation and demonstration, the formal TCM clinical epidemiology questionnaire on the etiology and syndrome differentiation in CAD was finalized, after which, the study protocol, inclusive and exclusive criteria and related quality control measures were prepared. The multiregional clinical epidemiological survey with more than 5,000 participants with CAD will be carried out in 41 TCM hospitals of China for investigating the TCM etiology and syndrome differentiation of CAD.

DISCUSSION: Multiregion large sample size clinical epidemiology survey on TCM etiology and syndrome differentiation in CAD will provide further evidence in preventing CAD and improving the standardization process of syndrome research.

TRIAL REGISTRATION: This study protocol was registered at the Chinese Clinical Trial Registration Center., doi: 10.3391/jcim.20120604

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Coronary artery disease (CAD) is a heart condition characterized by myocardial ischemia or necrosis caused by vascular stenosis or occlusion, or (and) coronary functional change (spasm). It belongs to the category of chest impediment, heart pain, real heart pain, palpitations, etc. in traditional Chinese medicine (TCM). CAD can be categorized into angina, myocardial infarction, heart failure, arrhythmias and sudden death. In recent years, some new concepts, such as acute coronary syndromes (ACS), unstable angina (UA), ST-segment-elevation myocardial infarction (STEMI) and non-ST-segment-elevation myocardial infarction (NSTEMI), have gained more emphasis. The development of this disease varies and advances rapidly, and has high incidence and mortality rate. Moreover, an increasing trend of incidence has been observed in the younger population recently. The increasing incidence of the disease has seriously threatened the health and life of the public.

Treatment design based on syndrome differentiation is important for diagnosis and treatment of TCM. As early as the eastern Han Dynasty, Zhang Zhongjing pointed out that weak pulse at Cun and wiry pulse at Chi is the etiology and pathogenesis of TCM of chest impediment and this theory is supplemented and developed in successive dynasties. However, as lifestyle changes, the current medical model has changed from the simple biological model to biopsychosocial model, resulting in increasingly complex etiology and risk factors for CAD. Consequently, the theory of weak pulse at Cun and wiry pulse at Chi has developed with new contemporary characteristics and needs to be proven by large clinical epidemiological study. Some TCM researchers have carried out related studies on the syndromes of CAD, which may to a certain extent increase the understanding of the distribution characteristics seen in CAD syndromes. However, lack of a large sample size and prospective design limits the overall understanding of syndrome characteristics of TCM and thus impedes the improvement of clinical efficacy of TCM for the disease.

Clinical epidemiology, a fundamental clinical science, introduces the related modern epidemiological and statistical theories into the clinical medical field for investigating the cause, risk factors, diagnosis, treatment and prognosis of this disease[1]. Epidemiological survey is a key clinical epidemiology research method, using self-administered questionnaires or structured interview to collect data from the specific group directly, and understand or prove a certain phenomenon or law through statistical data analysis[3]. With scientific design and standardized epidemiological survey, the authors want to explore TCM etiology and syndrome characteristics in CAD, which can be beneficial as a reference for the prevention and treatment of this disease.

A multiregion, large sample size clinical epidemiology survey on etiology and syndrome differentiation of TCM in CAD will be carried out, in order to (1) establish the database for CAD clinical epidemiology; (2) gain a profound understanding of the TCM etiology and risk factors of CAD; (3) discover the distribution of TCM syndrome...
characteristics in CAD.

1 Methods

1.1 Preliminary work

1.1.1 Literature review and analysis After reviewing TCM literature on the diagnosis and treatment of CAD through the China National Knowledge Infrastructure, VIP database for Chinese Technical Periodicals and Wanfang Data, a total of 1,034 items of relevant literature were obtained. After extracting the necessary information, a TCM diagnosis and treatment information database for CAD was established. It contained 190 items on TCM symptoms and tongue and pulse, among them, 100 items on inquiry, 35 items on inspection, 26 items on tongue diagnosis, 7 items on listening and smelling, 6 items on body palpation and 16 items on pulse diagnosis, which composed the item pool of the TCM diagnostic information. In the meantime, books entitled Traditional Chinese Medicine Etiology and Pathogenesis,[6] Basic Theory of Traditional Chinese Medicine,[1] Diagnostics of Traditional Chinese Medicine,[5] Internal Medicine of Traditional Chinese Medicine,[6] national standard Clinical Terminology of Traditional Chinese Medical Diagnosis and Treatment — Syndromes (GB/T 16751. 2-1997), Traditional Chinese Medicine Syndrome Differentiation Criteria of Coronary Heart Disease,[7] and Guidelines for Clinical Research on Chinese New Herbal Medicines (trial implementation) (2002 edition).[8] were referred to when designing the preliminary clinical questionnaire for TCM etiology and syndrome differentiation in CAD.

1.1.2 Clinical pre-survey Several rounds of pre-surveys were carried out by using a preliminary clinical questionnaire. Experts and clinical investigators summarized and analyzed the problems encountered during the course of each pre-survey so as to improve the CAD questionnaire. The reliability and validity of the CAD questionnaire were tested after each pre-survey in order to ensure the accuracy and clinical feasibility.

1.1.3 Expert consultation By Delphi method and analytic hierarchy process, the TCM etiology and syndrome for CAD questionnaire was sent out to 38 national experts in TCM cardiovascular diseases to seek their opinions, thus further improving the design of the questionnaire.

1.1.4 The formation of a formal questionnaire After three rounds of clinical pre-surveys, expert consultation and demonstration, necessary amendments were made and the questionnaire was constantly revised before the formal “TCM clinical epidemiology questionnaire on the etiology and syndromes of CAD” was finalized.

1.1.5 Formal clinical survey The study protocol, standards and related quality control measures will be prepared and the multiregional large sample clinical epidemiological survey will be held in more than 40 TCM hospitals in China.

1.2 Contents of the clinical survey

1.2.1 Participants The inpatients and outpatients diagnosed with CAD (chronic stable angina, UA, NSTEMI, acute STEMI, heart failure, cardiac arrhythmia, resuscitation of patients with sudden death and silent myocardial ischemia) will be included in this clinical epidemiological survey. All cases will be enrolled from December 2011 to June 2012.

1.2.2 Participating units Forty-one large-scale TCM hospitals from 23 provinces, municipalities and autonomous regions of China will participate in this research. The participating units and the corresponding codes are shown in Table 1.

1.2.3 Diagnostic Criteria Referring to the “Guidelines for the Diagnosis and Management of Chronic Stable Angina”[9] (2007 edition), “Guidelines for the Diagnosis and Management of Unstable Angina and Non-ST-segment Elevation Myocardial Infarction”[10] (2007 edition), “Guidelines for the Diagnosis and Management of Acute ST-segment Elevation Myocardial Infarction”[11] (2010 edition), “Guidelines for the Diagnosis and Management of Chronic Heart Failure”[12] (2007 edition) and “Chinese Expert Consensus on Diagnosis and Treatment for Heart Failure with Normal Left Ventricular Ejection Fraction”[13] , the CAD diagnostic criteria are as follows: (1) patients with more than 50% stenosis in at least one main branch of the coronary artery determined by coronary angiography (CAG) or computed tomography angiography (CTA), with or without angina, heart failure, arrhythmias, resuscitation after sudden death; (2) patients with clear evidence of ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction; (3) patients with a history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).

1.2.4 Inclusion and exclusion criteria

1.2.4.1 Inclusion criteria (1) Age more than 18 years; (2) meeting diagnostic criteria for CAD; (3) voluntarily join this study and sign informed consent.

1.2.4.2 Exclusion criteria (1) Rheumatic heart disease, pulmonary heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, myocarditis, severe valvular disease, hyperthyroidism, malignant tumor and hematopathy; (2) psychosis or dysgnesia; (3) declining to sign the informed consent.

1.2.5 Sample size In the multifactor statistical analysis, sample size is always 5 to 10 times of the number of variables[14]. In actual operation, in order to avoid or attempt to avoid false-positive and false-negative errors, a sample size of 20 to 30 times of the number of variables is usually required. The questionnaire contains approximately 200 variables. Considering the dropout rate of less than 15%, preliminary approximation of the total sample size is: $200 \times 20 + 200 \times 20 \times 15\% \approx 5,000$ cases.
1.2.6 Survey content  The survey content should include (1) informed consent page; (2) inclusion and exclusion criteria; (3) demographic characteristics: gender, age, nationality, marital status, highest qualification, nature of work, native place, place of residence, home address and zip code; (4) disease incidence: source of cases, chief complaint, predisposing factors, season (particular time) of occurrence or aggravation; (5) TCM symptoms: the main symptoms, head and body, eyes and ears, feeling of coldness or fever, perspiration, consciousness and quality of sleep, diet and appetite, stool and urine, body examination through inspection, listening and smelling and palpatory examination, tongue diagnosis, pulse diagnosis; (6) past medical history; (7) personal life history: the temperament characteristics, eating habits, food preference, daily life, smoking history and alcohol consumption history; (8) marriage, childbearing and menstrual history; (9) family history; (10) physical examination; (11) TCM diagnosis; (12) clinical diagnosis; (13) laboratory tests: blood glucose, blood lipids, liver and kidney function, coagulation function, serum cardiac creatinine, myocardial injury markers, brain natriuretic peptide, C-reactive protein, thyroid function, electrocardiogram, echocardiography, CAG or CTA; (14) condition of survey completion.

1.3 Quality control measures  Quality control is important for the successful execution of research, which can be done by preparing standard operation procedures (SOPs), providing systematic training for investigators, increasing patient compliance, strictly implementing inclusion and exclusion criteria, standardizing the completion of questionnaires, and so on. Enhancing quality control during the whole process will ensure the authenticity and reliability of the survey.

1.3.1 Standardizing the collection of TCM information  While collecting information of the patients, relatively standardized Chinese medicine termi-
nologies should be used, and the language should be comprehensible. The investigator has to listen patiently and record information objectively, so as to avoid any omission of information and to collect comprehensive clinical data. Observation of the tongue and body should be done under sufficient natural light and should avoid interference by colored light. Body parts to be examined should be fully exposed. Each tongue observation should not last for more than 30 s. If the initial observation was not satisfactory, the patient is allowed to rest for a moment before observing again. In the investigator’s brochure, colorized tongue contrast map is supplied as a reference for TCM diagnosis. Pulse diagnosis is to be conducted at the radial artery using specific techniques.

1.3.2 Training of investigators Training of investigators includes two courses: concentrated training sessions and CD disk guidance. Specific training contents include: (1) aim, method and specific contents of the survey; (2) related SOPs; (3) standardization of questionnaire completion; (4) information and data management; (5) other related content.

1.3.3 Assurance of patient compliance For improving patient compliance, the investigators should (1) inform the aim of the survey to the patients and seek informed consent actively; (2) select appropriate survey environment and maintain friendly attitude; (3) accept the medical consultation from survey object, and answer with patience in detail; (4) strengthen the guidance of the health education for CAD patients.

1.3.4 Standardization of questionnaire completion (1) Before starting the survey, read the content of the questionnaire and implementation program carefully. Be familiar with the process of filling in the form. (2) According to the unified method of recording, fill in each item according to the order seriously, accurately and clearly. (3) After the survey, look through the questionnaire to make sure that there are no omissions and no mistakes, avoid inconsistency of information or logic errors. Should there be any mistake, correct them immediately. (4) If the contents of the questionnaire require modification or correction, standardized editing methods should be used. Do not use correction fluid. Do not shade wrong words beyond recognition. Cancellation is to be done only once in the middle of word and the edited content should be written beside it together with the signature of the investigator editing the information and time.

1.3.5 Supervision and internal inspection (1) The clinical monitor authorized by the project leader will carry out on site and telephone supervision randomly on the participating units, after which, write a supervision report. (2) The person in charge of each participating unit will assign a quality control administrator, who will carry out periodic internal inspection. If problems are discovered, he should communicate with the investigator immediately to work out solutions, so as to ensure the authenticity and reliability of the survey. (3) If the quality control administrator encounters problems or queries, he/she can consult the project monitor or study group members of the survey through email, telephone or fax. (4) Quality control and clinical supervision include the progress of the study, signing of informed consent forms, standardized completion of questionnaires, as well as consistency of survey contents and raw data.

1.3.6 Information management

1.3.6.1 Digital coding Every participating unit corresponds to a 3-digit code. According to the order of registration, investigating case codes will be generated, for example, the first case recruited for participating unit 001 will be 001-001.

1.3.6.2 Dynamic management Tengxun software “diary management” will be used for dynamic data management. The investigation groups have an individual Tengxun account number allocated to them, with username and password. After completing each investigation, investigators are to log in “diary management” and register the case.

1.3.6.3 Data acquisition In order to ensure the accuracy and objectivity of the survey data, it is recommended that, two or more trained and qualified investigators are present in the clinical surveys. The data acquisition, especially the subjective judgment, such as tongue and pulse, requires consensus from both investigators in order to reduce biasness. If necessary, a third person can assist.

1.3.6.4 Data questioned (1) The finished questionnaire will be checked by a project monitor. If there are doubts on the questionnaire, the data clarification form (DCF) will be completed; (2) the DCF and questionnaire will be sent back to the original survey units; (3) investigators need to fully explain, supplement and amend; (4) when necessary, may require the monitor to resend DCF.

1.3.6.5 Data entry and management (1) Relatively independent data management group is set up by the data administrator; (2) all the data will be transferred to the data management group and unified computer entry; (3) data entry with double entry method, make a backup in case of loss; (4) real-time data entry to amend, update, and improve the database.

1.4 Ethics review The program, in line with the Declaration of Helsinki on the relevant provisions for the rights protection of research subjects, has been reviewed and approved by the ethics committee of the First Teaching Hospital of Tianjin University of TCM (Ethics approval document: TYLL2011 [ K ] 004). The personal information and privacy of the patients will be strictly protected, and they have right to sign informed consent and to withdraw at any time during the course of the survey. The flow chart of
this trial is shown in Figure 1.

1.5 Statistical methods EpiData will be used to create the database and SPSS 16.0 will be used for statistical analysis. Frequency analysis, factor analysis, cluster analysis, correlation analysis, logistic regression analysis, and other statistical methods will be selected for the data processing.

2 Discussion

With the progression of science and technology, more advanced methods and techniques have been applied for the diagnosis and treatment of CAD. The treatment modalities for CAD, including drugs, PCI and CABG, have improved greatly. However, concurrently, we are facing numerous additional medical problems, such as myocardial no-reflow and restenosis after PCI. With the characteristics of multilink, multilevel and multitarget, TCM emphasizes the concept of holism and treatment based on syndrome differentiation, which might provide innovative ideas and approaches for the above clinical problems. Related research suggests that, TCM not only plays an important role in restenosis after PCI[15,16], myocardial no-reflow[17,18], but also helps in the protection of vascular endothelial cells[19,20], the stability of coronary artery plaque[21,22] and angiogenesis[23,24], and contributes to the improvement of quality of the patient’s life[25,26]. Therefore, it has become a pressing issue to determine the method to study the TCM etiology and syndrome characteristics of CAD more effectively in order to implement TCM interventions more scientifically and reasonably. This is an essential step to further improve the level of clinical diagnosis and treatment for CAD.

Through rigorous scientific study design, epidemiological and statistical methods are introduced into the TCM clinical research of CAD. With the background of previous preliminary work such as literature analysis, expert consultation and clinical pre-survey, the authors designed the TCM clinical epidemiology questionnaire on the etiology and syndromes of CAD, and related procedures to implement the program, standard operating procedures and quality-control measures. A nationwide clinical epidemiology survey with a large sample size will be launched multiregionally, so as to explore the TCM etiology and syndrome characteristics of CAD in depth. By creating a CAD clinical epidemiology database, further studies of the TCM etiology and syndrome characteristics of CAD could provide reference for the prevention and treatment of CAD, which would be beneficial in improving the clinical efficacy for this disease.

Figure 1  The general process of clinical epidemiology survey of TCM etiology and syndrome differentiation of CAD

TCM: traditional Chinese medicine; CAD: coronary artery disease.


3 Competing interests

The authors declare that they have no competing interests.

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“冠心病中医药病因及证候临床流行病学调查”的研究方案

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背景：冠心病属于临床常见疾病，具有较高的发病率和死亡率，严重影响人民的健康和生命。中医药在冠心病的预防和治疗中发挥着重要作用，通过临床流行病学调查，掌握冠心病的中医病因和证候分布特征，将有利于进一步提高该病的中医临床疗效。

方法与设计：经过文献回顾与分析，初步建立冠心病中医病因及证候临床流行病学调查表，随后通过多次临床预调查显示专家咨询，论证，制定正式的冠心病中医病因及证候临床流行病学调查表，并修订实施方案，相关规范及质量控制措施。采用冠心病中医病因及证候临床流行病学调查表在全国范围内开展多地域、大样本的冠心病中医临床流行病学调查研究。

讨论：通过多地域，大样本的冠心病中医临床流行病学调查，了解我国冠心病的中医病因及证候分布特征，可为冠心病的临床预防及中医辨治提供参考依据，也有利于提高中医病证研究的科学化与规范化水平。

临床试验注册号：研究方案于 2011 年 11 月 27 日在中國临床试验注册中心进行中英文注册，注册号为 ChiCTR-ECS-11001728。

关键词：冠心病；中医；中医病因；证候；流行病学研究；问卷调查；多中心研究；临床方案

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中国中西医结合学会虚证与老年医学专业委员会拟定于 2012 年 10 月在广东省会举行“第六届虚证与老年医学专业委员会成立大会暨第十二次学术研讨会”，现将会议征文通知如下。

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