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Comparison of antiangina therapies in patients with coronary heart disease in China: study protocol for a multicentre, retrospective, hospital system-based study

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ABSTRACT

Introduction China has the largest number of patients with coronary heart disease (CHD) in the world. Numerous pharmacological strategies are available for CHD in routine clinical practice. CHD-induced angina pectoris affects patients' quality of life and is a key predictor of prognosis. This study will compare the effectiveness of different antiangina treatments, particularly ATP-sensitive potassium channel (K_{ATP}) activators, in the Central China District. This proposal underpins the first comparison of antiangina therapies in patients with CHD in China using a multicentre, retrospective, hospital system-based assessment.

Methods and analysis This retrospective real-world study will assess the largest hospital databases in Wuhan City in Central China to evaluate outcomes including mortality, revascularisation, myocardial infarction (MI), stroke and other cardio-cerebrovascular events in patients with CHD. Data will be consecutively collected between 1 April 2009 and 31 August 2019 through the hospital information system, laboratory information system and hospital imaging system. All data will be standardised by at least three independent technicians and statisticians using International Classification of Diseases Tenth Version, ISO15189 and Specification for Drafting of Basic Dataset of Electronic Medical Record (WS445). The data will include patient demographics, physical and laboratory examinations, imaging examinations, medical history, diagnosis, treatment options and payment information. We will compare K_{ATP} activators with other antiangina drugs using propensity score matching. The primary outcome will be major adverse cardiovascular events, defined as a composite of death, MI, stroke and rehospitalisation due to angina.

Ethics and dissemination The current study is designed to translate research into improved care for patients. The institutional review board of Wuhan Tongji Hospital (Liao Jiazhi, Du Aiye, Chen Zhishui, Fang Feng, Yu Shiying, Liu Dong and Li Yaping) approved the study protocol (version 1.0, July 2019, approval number TJ-IRB201909112). Here we reported a protocol related to a pre-results. Data will be presented in peer-reviewed journals, social media and relevant conferences.

Trial registration number ChiCTR1900027812; Pre-results.

Strengths and limitations of this study

- This is the first largest assessment of the effectiveness of various antiangina treatments using Chinese hospital system databases, permitting the analysis of ~180 000 patients over a 10-year period in a real clinical setting.
- This study will fill the gap in studies of patients with angina in Central China, who have received lack of attention in previous large-scale clinical studies.
- Unavoidable limitations of the current study include low data accuracy compared with clinical trials and large percentage of lost-to-follow-ups in real-world situation.
- In China's public hospitals, outpatient and inpatient clinical information systems are often from different manufacturers, so it is too difficult to match patients' data from different systems until data exchange has been realised in recent years.
- We can trace major adverse cardiovascular events (MACE) record from three hospital information systems, but information about patients undergoing MACE treatment in other hospitals will not be obtained.

INTRODUCTION

Globally, coronary heart disease (CHD) causes the largest number of deaths. China has the largest CHD population, with one in five deaths resulting from vascular disease.[1–3] As the population of China ages, cardiovascular risk factors will increase in prevalence. CHD symptoms often result from angina pectoris (AP), leading to a high disease burden.[3 4]

Almost 50% of patients with CHD have angina,[5] which demonstrates typical symptoms of chest pain.[6] Currently, the management of stable angina includes preventive and medical therapy. Preventive therapies include aspirin, blood pressure control and lifestyle behaviours. Medical therapy includes

a combination of two antiangina therapies from different drug classes (β-blockers, Ca^{2+} channel, blockers, nitrates or ATP-sensitive potassium channel (K_{ATP}) activators).[5] For patients with obstructive CHD, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are recommended.[7–9] However, following PCI or CABG, angina persists and major adverse cardiovascular events (MACEs) are reported in up to 15%–20% of patients.[10 11] These residual risk factors are primarily due to coronary microvascular dysfunction (CMVD), which is assumed to be responsible when other causes of angina have been discounted. New CMVD therapeutics are therefore urgently required.[12–14]

Nicorandil, a classic K_{ATP} activator, is widely used for AP therapy. Nicorandil dilates normal and stenosis segments of the coronary arteries, without the production of coronary steal.[15–19] Nicorandil can improve clinical outcomes in terms of acute myocardial infarction[20] to improve coronary reflow[21] and cardiac pump function,[22] relieve angina,[23] reduce myocardial injury,[24] and reduce cardiovascular events.[25]

Nicorandil and nitrates are second-line therapies according to current clinical guidelines.[26] However, meta-analyses show that all antiangina drugs have similar efficacy in reducing symptoms, and it is suggested that second-choice drugs have more evidence-based clinical data that are more contemporary than are available for traditional first-choice drugs.[27] Nicorandil has been demonstrated to provide survival benefits in various studies,[28–30] while nitrates are the most frequently prescribed second-line antiangina drug in China. Therefore, comparisons between these two drugs are valuable to provide clinical suggestions for physicians in choosing second-line antiangina therapies.

Although clinical trials highlight the benefits of nicorandil in patients with CHD, its long-term effectiveness and safety have not been determined in the Chinese population. This article presents a retrospective real-world study in the Central China District using hospital databases to evaluate the long-term effectiveness and safety of nicorandil in patients with CHD. We herein describe the database systems and statistical methods to minimise bias in the comparison of rates of MACE between nicorandil and other antiangina pharmacological strategies.

METHODS AND ANALYSIS

Design overview

Databases from three hospitals in Wuhan will be used for this study, and ethical approval has been obtained from Wuhan Tongji Hospital (Ethics Committee: Liao Jiazhi, Du Aiye, Chen Zhishui, Fang Feng, Yu Shiying, Liu Dong and Li Yaping; approval number TJ-IRB201909112). Data will be consecutively collected between 1 April 2009 and 31 August 2019 from the hospital information system (HIS), laboratory information system (LIS) and hospital imaging system. Analysis of CHD cohorts with regard to the effectiveness and safety of K_{ATP} activators versus other angina medications will be conducted. Selection bias will be minimised by minimal inclusion and exclusion criteria. Statistical methods including propensity score matching will be applied to reduce confounding.

Population

Patients fulfilling the following inclusion and exclusion criteria will be consecutively enrolled and their data in the hospital databases will be used in the study:

Inclusion criteria

- Aged ≥18 years.
- Clinically diagnosed with CHD.
- Receiving antiangina therapy.

Exclusion criteria

- Previous cardiac transplant or valve surgery.
- Pregnancy.

Outcome assessments

The primary outcome is the rate of MACE at 3 years, where MACE is defined as a composite of myocardial infarction (MI), stroke, rehospitalisation due to angina and death.[31 32]

Secondary and explorative effectiveness outcomes included the following:

- Rate of MACE at 1, 5 and 10 years.
- Rate of bleeding event if combined with aspirin.
- Rate of hypertension combined with angiotensin-converting enzyme (ACE) inhibitor (ACEI)/angiotensin II receptor blockers (ARB).
- Rate of liver dysfunction combined with statins.
- Other crucial clinical outcomes, including rehospitalisation duration, cost of rehospitalisation and rate of drug discontinuation.

Safety outcomes included the following:

- Reported adverse events.
- Reported drug tolerance.
- Abnormal laboratory results.

Data collection

Data from patients with CHD, aged ≥18 years, will be included, encompassing 150 000 individuals. Data accessed from hospital databases included demographics, medical history, antiangina drug data, laboratory data, hospitalisation expenses, hospitalisation time limits, drug combinations and individual MACE events. Only patients clinically diagnosed with CHD will be enrolled. Antiangina therapy will be assessed from stored prescription databases.

We will investigate the discharge diagnoses of patients with coronary artery disease and postmenopausal female patients with a high risk of coronary microvascular obstruction. Data on these patients were collected from the outpatient medical records. We collected patient information from HIS, electronic medical record system, LIS and radiology information system, including inpatient registration sheets, discharge diagnosis sheets, medication administration records, laboratory tests and outpatient

clinical records. Data were connected to patient number, and data merging, data filling, deduplication and integration will be performed. All data will be collected following the approval of our independent ethics committee. We collected baseline characteristics, comorbidities, treatment patterns, prescribed therapies (daily aspirin doses, daily ACEI/ARB/β-blocker doses, daily calcium channel blocker (CCB) doses, daily nitrate doses and daily statin doses). The characteristics of patients enrolled in the registries will be collected (age, gender, identity card number, type of practice, medical history, geographical location, risk factors, type of angina, coronary angiography data, cardiovascular therapeutic drugs, type of MI and other adverse cardiovascular events). We will also collect data on adverse events and serious adverse events.

Data management

Site data will be collected from the hospitals and forwarded to the central clinical research database. Data management for the registry study will be performed by an independent third party (Le9 Health Technology, Shanghai). The third party will systematically perform data analysis and remove invalid values and outliers. If a data query is made, the relevant records will be traced and reviewed. The third party will be responsible for the protection of patient information, accuracy, study sites and adherence to protocol requirements.

Data elements

We will search online databases for English clinical studies on cardiovascular disease and nicorandil. We will supplement the search with a list of candidate variables according to physicians' clinical experience. Table 1 highlights the major study categories. We defined all variables prior to data analysis. Key endpoint variables were defined, including death, MI, stroke and hospitalisation due to angina attack (refer to the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials).

Table 1 Data elements

Data	Baseline	6 months	1 year and thereafter
Demographics	√		
Medical history	√		
Laboratory test	√	√	√
Physical examination	√		
Medication recording	√	√	√
Surgery procedures	√	√	√
Image procedures	√	√	√
Medical insurance status	√		
Socioeconomic status	√		
Clinical outcomes			
Major adverse cardiovascular events		√	√
Death		√	√
Rehospitalisation		√	√
Stroke		√	√
Myocardial infarction		√	√
Adverse events		√	√

Statistical analysis

Data will be shown as mean (SD) and median for continuous data. For categorical data, values will be shown as % or counts. We will statistically assess all continuous variables using Kolmogorov-Smirnov tests. Normally distributed data will be shown as mean±SD and analysed by t-test or one-way analysis of variance assessments. Non-normal data will be shown as median with IQR and analysed using standard non-parametric methods. Discrete variables will be compared using X^2 tests. It is likely that the characteristics of the patients and the physicians, risk of CHD, therapies and outcomes will correlate with each institution, and as such clustering analysis will be performed. We will employ models including logistic, linear, Cox proportional hazards and Poisson distributions to investigate and adjust intergroup differences. P values less than 0.05 will be considered significant.

We anticipate the following analytical protocols: (1) patient demographics and CHD risk factors; (2) evaluation of 12-month major cardiovascular events (MI, stroke, rehospitalisation, death, revascularisation) in relation to K_{ATP} activator use for CHD; (3) comparisons of other clinical benefits (drug tolerance, duration of rehospitalisation, rehospitalisation expense); and (4) comparisons of adverse events and antiangina drug discontinuation according to antiangina therapy.

Sample size

Assuming the rates of MACE are approximately 13.1% and 15.5% in the K_{ATP} activator group and the non-K_{ATP} activator group,[28 33] respectively, 2129 patients in the K_{ATP} activator group (group sample size ratio at 1:4 after propensity score matching) will be required to provide 80% power at a two-sided significant level of 0.05. Considering that the number of patients using K_{ATP} activator in the three hospitals is far more than 2129 and the number of patients not using K_{ATP} activator is far more than 8515, we will include all patients meeting the inclusion and exclusion criteria.

ETHICS AND DISSEMINATION

Required ethics approvals have been obtained from associated institutions (Ethics Committee of Wuhan Tongji Hospital: Liao Jiazhi, Du Aiye, Chen Zhishui, Fang Feng, Yu Shiying, Liu Dong and Li Yaping). Le9 Health Technology (Shanghai) will control all data handling. Data access, privacy and research service agreements have been completed. Data will be published in a manuscript in appropriate peer-reviewed journals.

START AND END DATES OF THE STUDY

The start dates of this study in Tongji Hospital, Union Hospital and Wuhan Central Hospital are 20 September 2019, 28 May 2020, and 30 October 2019, and the end date is 31 September 2020.

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Contributors NZ, ZK and JH made substantial contributions to study conception. NZ and LS designed and supervised the study. PL, JC and NZ collected patients' data, provided administrative, technical and material support, and drafted the manuscript for important intellectual content. LS and JH completed the statistical analysis of the data.

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