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

Ping Li,1 Juan Chen,2 Zheng Ke,3 Jing Han,3 Lan Shen 4, Ning Zhou 5

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<sub>ATP</sub>) 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<sub>ATP</sub> 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 Jiazi, Du Aiye, Chen Zhishui, Fang Feng, Yu Shiyang, 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.

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.4–6

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, Ca²⁺ channel blockers, nitrates or ATP-sensitive potassium channel (Kᵦᵦᵦ) activators). For patients with obstructive CHD, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are recommended. However, following PCI or CABG, angina persists and major adverse cardiovascular events (MACEs) are reported in up to 15%–20% of patients. 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.

Nicorandil, a classic Kᵦᵦᵦ activator, is widely used for AP therapy. Nicorandil dilates normal and stenosis segments of the coronary arteries, without the production of coronary steal. Nicorandil can improve clinical outcomes in terms of acute myocardial infarction to improve coronary reflow and cardiac pump function, relieve angina, reduce myocardial injury, and reduce cardiovascular events.

Nicorandil and nitrates are second-line therapies according to current clinical guidelines. 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. Nicorandil has been demonstrated to provide survival benefits in various studies 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 Aiyi, Chen Zhishui, Fang Feng, Yu Shiying, Liu Dong and Li Yaping; approval number TJ-JRB201909112). 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 Kᵦᵦᵦ 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.

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 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).

**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 X² 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 demographies and CHD risk factors; (2) evaluation of 12-month major cardiovascular events (MI, stroke, rehospitalisation, death, revascularisation) in relation to K<sub>ATP</sub> 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<sub>ATP</sub> activator group and the non-K<sub>ATP</sub> activator group, respectively, 2129 patients in the K<sub>ATP</sub> 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<sub>ATP</sub> activator in the three hospitals is far more than 2129 and the number of patients not using K<sub>ATP</sub> 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 Shiyiing, 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.

Author affiliations
1Department of Cardiothoracic Surgery, Union Hospital, Huazhong University of Science and Technology, Wuhan, China
2Department of Cardiology, Tongji Hospital of Tongji University, Wuhan, China
3Division of Cardiology, Shanghai Chest Hospital, Shanghai, China
4Medical Department, Chugai Pharma China, Shanghai, China
5Division of Cardiology, Department of Internal Medicine, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China

Acknowledgements The authors are grateful to Xiang You, Xinxin Chen, Kailing Liu and Lei Mo, Le9 Health Technology (Shanghai), for assistance during clinical data extraction.

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.

Funding This work was supported by grants from the National Natural Science Foundation of China (no. 81570261).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Lan Shen http://orcid.org/0000-0002-1579-4013
Ning Zhou http://orcid.org/0000-0003-0863-3091

REFERENCES
1 Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the American Heart Association. Circulation 2015;131:e29–322.
2 Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet 2019;394:1145–58.
3 Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304:1350–7.
4 Yang G, Kong L, Zhao W, et al. Emergence of chronic non-communicable diseases in China. Lancet 2008;372:1697–705.
5 Ohman EM. Chronic stable angina. N Engl J Med 2016;375:1167–76.
6 Valgimigli M, Biscaglia S. Stable angina pectoris. Curr Atheroscler Rep 2014;16:422.
7 Banning AP, Baumbach A, Blackman D, et al. Percutaneous coronary intervention in the UK: recommendations for good practice 2015. Heart 2015;101:1–13.
8 Stone GW, Sabik JF, Serruys PW, et al. Everolimus-Eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223–35.
9 Sousa-Uva M, Head SJ, Milojiciv M, et al. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg 2018;53:5–33.
10 Shroyer AL, Hattler B, Wagner TH, et al. Five-year outcomes after on-pump and off-pump coronary-artery bypass. N Engl J Med 2017;377:623–32.
11 Thiele H, Akin I, Sandri M, et al. One-year outcomes after PCI strategies in cardiogenic shock. N Engl J Med 2018;379:1699–710.
12 Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830–40.
13 Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. Circulation 2010;121:2317–25.
14 Rahman H, Corcoran D, Aetseam-Ur-Rahman M, et al. Diagnosis of patients with angina and non-obstructive coronary disease in the catheter laboratory. Heart 2019;105:1536–42.
15 Frydmann AM, Chapelle P, Diekmann H, et al. Pharmacokinetics of nicorandil. Am J Cardiol 1989;63:253–33.
16 Zhu H, Xu X, Fang X, et al. Effects of mitochondrial ATP-sensitive potassium channel activation (nicorandil) in patients with angina pectoris undergoing elective percutaneous coronary interventions: a meta-analysis of randomized controlled trials. Medicine 2019;98:e14165.
17 Rajaratnam R, Birger DB, Hawkins R, et al. Attenuation of anti-ischemic efficacy during chronic therapy with nicorandil in patients with stable angina pectoris. Am J Cardiol 1999;83:1120–4.
18 Suryapranata H. Coronary haemodynamics and vasodilatory profile of a potassium channel opener in patients with coronary artery disease. Eur Heart J 1993;14:16–21.
19 Sakai K, Shiraki Y, Nabata H. Cardiovascular effects of a new coronary vasodilator N-(2-hydroxyethyl)nicotinamide nitrate (SG-75): comparison with nitroglycerin and diltiazem. J Cardiovasc Pharmacol 1981;3:139–50.
20 Wu M, Huang Z, Xie H, et al. Nicorandil in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis. PLoS One 2013;8:e78231.
21 Okamura A, Rakugi H, Ohashi M, et al. Additive effects of nicorandil on coronary flow during continuous administration of nitroglycerin. J Am Coll Cardiol 2001;37:719–25.
22 Zhao F, Chaugai S, Chen P, et al. Effect of nicorandil in patients with heart failure: a systematic review and meta-analysis. Cardiovasc Ther 2014;32:283–96.
23 Secco GG, Parisi R, Mirabelli F, et al. Old and new drugs for treatment of stable angina: new anti-anginal drugs and coronary revascularization. Cardiovasc Hematol Agents Med Chem 2015;13:21–4.
24 Ye Z, Su Q, Li L. The clinical effect of nicorandil on periperal myocardial protection in patients undergoing elective PCI: a systematic review and meta-analysis. Sci Rep 2017;7:45117.
25 Luo B, Wu P, Bu T, et al. All-cause mortality and cardiovascular events with nicorandil in patients with IHF: systematic review and meta-analysis of the literature. Int J Cardiol 2014;176:661–9.
26 Knudt J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–77.
27 Ferrari R, Camici PG, Crea F, et al. Expert consensus document: A ‘diamond’ approach to personalized treatment of angina. Nat Rev Cardiol 2018;15:120–32.
28 IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the impact of nicorandil in angina (IONA) randomised trial. Lancet 2002;359:1269–75.
29 Horinaka S, Yabe A, Yagi H, et al. Effects of nicorandil on cardiovascular events in patients with coronary artery disease in the Japanese coronary artery disease (JCAD) study. Circ J 2010;74:503–9.
30 Sakata Y, Nakatani D, Shimizu M, et al. Oral treatment with nicorandil at discharge is associated with reduced mortality after acute myocardial infarction. J Cardiol 2012;59:14–21.
31 Xu H, Zou J, Ye X, et al. Impacts of clinical pharmacist intervention on the secondary prevention of coronary heart disease: a randomized controlled clinical study. Front Pharmacol 2019;10:1112.
32 Jukema JW, Szarek M, Zijlstra LE, et al. Alirocumab in Patients With Polycythaemia and Recent Acute Coronary Syndrome: ODYSSEY OUTCOMES Trial. J Am Coll Cardiol 2019;74:1167–76.
33 IONA Study Group. Impact of nicorandil in angina: subgroup analyses. Heart 2004;90:1427–30.