PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol of the China ST-segment elevation myocardial infarction (STEMI) Care Project (CSCAP): a 10-year project to improve quality of care by building up a regional STEMI care network
AUTHORS	Zhang, Yan; Yu, Bo; Han, YL; Wang, Jianan; Yang, Lixia; Wan, Zheng; Zhang, Zheng; Chen, Yu-guo; Fu, Xianghua; Gao, Chuanyu; Li, Bao; Chen, Ji-yan; Wu, Ming; Ma, Yitong; Zhao, Xingsheng; Chen, Yundai; Yan, Hongbing; Xiang, Dingcheng; Fang, Weiyi; Mehta, Sameer; Naber, Christoph K; Ge, Junbo; Huo, Yong

VERSION 1 - REVIEW

REVIEWER	Benedek Theodora University of Medicine and Pharmacy Tirgu Mures, Romania
REVIEW RETURNED	24-Sep-2018

GENERAL COMMENTS	The article is a good presentation of a relevant study design, on a STEMI dedicated protocol for a large population and the authors should be congratulated for their substantial effort to implement such a registry in this large area. However, the main message of the manuscript is not clear enough, therefore several corrections are necessary before considering the article for publication. I recommend publication after major revision, with the following aspects to be included in the revised version: The main problem is that the entire study seems more like an implementation project (for implementing modern STEMI treatment in China), instead of a research study. I recommend to rephrase the main objective of the study: instead of “to build up different types of integrated STEMI care networks” the objective should be “to show how implementation of different types of integrated regional STEMI networks can lead to mortality reduction”. The authors describe how they implement the system on 3 levels, but there are limited data on the clinical outcomes following this implementation. A coherent strategy to assess these outcomes is not clearly presented even if the data are present in the tables. The article should be more focused on the interventions to be measured and the outcomes to be measured, with precise timelines for outcome assessment. Also, it is not clear why the authors decided to include all STEMI patients (including those with STEMI occurrence within 30 days regardless of reperfusion therapy). This should be explained, as this is an approach different from the guidelines. There are also several minor concerns:

	1. As stated in the instructions for authors, at the end of the abstract the strengths and limitations of the study should be presented in bullet point format (max 5), instead of narrative way. 2. The English language should be polished – for instance, in the abstract: “And the CSCAP included…”, or on page 7 line 6: “the disease burden of cardiovascular diseases” (repetitions) 3. Please mention/provide the approval from the ethics committee 4. The study protocol should be registered first on a public platform – please see the instructions for authors 5. Please make sure that you do not confuse the “Stent for Life” initiative of the European Society of Cardiolpgy with the “Stent – save a Life” term 6. What is the scheduled timeline of this project? Please mention the entire duration of the study, as projected, and the time when the outcomes resulting from model implementation will be measured. 7. How were the 53 tertiary hospitals selected for the study? The authors mention that they were qualified for PPCI, but on what basis? The number of procedures, the experience of the operators? Also, please include the information if these hospitals are able to provide 24/7 pPCI, as this is extremely relevant for general AMI-related mortality. 8. “Routine clinical assessment and treatment” should be precisely presented – PCI? Statins, antiplatelet, etc… (page 11). 9. The ethics and dissemination part is too long and contains un-necessary discussions, instead of ethical and safety considerations. This should be significantly shortened, remaining only the part related to safety and limitations of the study. 10. A similar approach was presented in a study by Orzan et al (Impact of a Preexisting STEMI Network in Improving STEMI Diagnostic and Treatment in the Community after the Introduction of a National Program of Interventional Treatment in Acute Myocardial Infarction, Journal of Cardiovascular Emergencies, 2015; 1:23-28, DOI: 10.1515/jce-2015-0004), showing significant mortality reduction after implementation of a STEMI network. This should be referenced and commented.

REVIEWER	prof. Menko Jan de Boer Department of cardiology Radboud University Medical Center Nijmegen The Netherlands
REVIEW RETURNED	24-Oct-2018

GENERAL COMMENTS	This is a description of collecting data on STEMI prospectively. No clinical data are presented although the registry started in 2011

REVIEWER	Edward Koifman Soroka University Medical Center, Israel
REVIEW RETURNED	21-Dec-2018

GENERAL COMMENTS	The authors present a study protocol of STEMI network in China. The subject is interesting and deserves attention, and data derived from this registry could impact the health care in China and other places. To my understanding the study is still ongoing, as such I would suggest to authors to provide the number of patients they plan to

	enroll in each phase and verify that this will enable them to have enough statistical power to reach solid conclusions regarding treatment interventions. Also, it is not clear enough what is the medical insurance system in China, how it affects care, and whether it is collected in the database.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Benedek Theodora

Institution and Country: University of Medicine and Pharmacy Tirgu Mures, Romania

Please state any competing interests or state ‘None declared’: none declared

Response: We appreciate the positive comments about the manuscript. The information of declaration has been added at the end of the manuscript as following.

“Competing interests None declared.”

Please leave your comments for the authors below

The article is a good presentation of a relevant study design, on a STEMI dedicated protocol for a large population and the authors should be congratulated for their substantial effort to implement such a registry in this large area.

However, the main message of the manuscript is not clear enough, therefore several corrections are necessary before considering the article for publication. I recommend publication after major revision, with the following aspects to be included in the revised version:

The main problem is that the entire study seems more like an implementation project (for implementing modern STEMI treatment in China), instead of a research study. I recommend to rephrase the main objective of the study: instead of “to build up different types of integrated STEMI care networks” the objective should be “to show how implementation of different types of integrated regional STEMI networks can lead to mortality reduction”. The authors describe how they implement the system on 3 levels, but there are limited data on the clinical outcomes following this implementation. A coherent strategy to assess these outcomes is not clearly presented even if the data are present in the tables. The article should be more focused on the interventions to be measured and the outcomes to be measured, with precise timelines for outcome assessment. Also, it is not clear why the authors decided to include all STEMI patients (including those with STEMI occurrence within 30 days regardless of reperfusion therapy). This should be explained, as this is an approach different from the guidelines.

Response: We appreciate the reviewer’s enthusiasm for our proposed study and thanks for your constructive comments. As the reviewer mentioned, the 10-year CSCAP project is not a study to access special intervention methods such as novel medications and devices but a project to implement guideline recommendations for improvement of quality of STEMI care by building up integrated regional networks in China.

According to your suggestion, we revised the main objective as below.

“To show how implementation of different types of integrated regional STEMI care networks can improve the reperfusion ratio, shorten the total duration of myocardial ischemia, and lead to mortality reduction step by step.”

STEMI patients benefit from both increasing reperfusion ratio and shortening of the duration from the symptom occurrence to the opening of the target vessel. In each CSCAP phase, the major process outcomes are different but have internal logic. Except the indexes of reperfusion ratio and method evaluated in each phase, different treatment delay indexes are selected in each phase which will shift to others step by step according to the stage of network construction. Door-to-balloon time (D2B) and Door-to-needle time (D2N), defined as from in-hospital FMC to target vessel open, are two major indexes to evaluate in-hospital delay in CSCAP-1. First medical contact-to-balloon time (FMC2B) and First medical contact-to-needle time (FMC2N) time, defined as FMC by emergency system or hospital to target vessel open, are used to evaluate the whole medical system delay in CSCAP-2. Total ischemic time, defined as from symptom onset to target vessel open, is used in CSCAP-3 to add the information of patient delay. Cardiovascular outcomes including mortality, non-fatal re-infarction, non-fatal stroke, heart failure and hospitalization due to cardiovascular reasons are also evaluated in each phase of CSCAP. We have added some sentences in the Methods and analysis section as below.

“These KPIs are different in each phase but have internal logic. Except reperfusion rate, method and cardiovascular outcomes, different treatment delay indexes are selected in different phases which will shift to others step by step according to the progress of network construction. D2N and D2B time, defined as from in-hospital FMC to target vessel open, were used to evaluate in-hospital delay in CSCAP-1. First medical contact-to-balloon time (FMC2B) and first medical contact-to-needle time (FMC2N) time, defined as FMC by emergency system or hospital to target vessel open, were used to evaluate the whole medical system delay in CSCAP-2. Total ischemic time, defined as from symptom onset to target vessel open, is used in CSCAP-3 to add the information of patient delay.”

Reperfusion is the key strategy to improve STEMI outcomes and is indicated in all patients with symptom onset within 12 h duration and persistent ST-segment elevation. Many patients miss the chance to receive timely reperfusion mainly due to lack of awareness. China PEACE study showed that it will take STEMI patients 13-15 hours from symptom onset to arrive in hospital in China in last decade [1]. Total ischemic time, the ultimate goal of treatment delay to be shorten, contains both patient delay and system delay. Public education is one of the important parts in our project. Thus, we include those patients with late admission to hospitals for the purpose of exploring optimal methods to shorten total ischemic time. We have added some sentences in the Methods and analysis section as below.

“STEMI patients with late admission to hospitals were also considered for the purpose of exploring optimal methods to shorten total ischemic time containing both patient delay and system delay.”

Reference

1. Li J, Li X, Wang Q, Hu S, Wang Y, Masoudi FA, Spertus JA, Krumholz HM, Jiang L; China PEACE Collaborative Group. ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): a retrospective analysis of hospital data. Lancet. 2015;385(9966):441-51.

There are also several minor concerns:

1. As stated in the instructions for authors, at the end of the abstract the strengths and limitations of the study should be presented in bullet point format (max 5), instead of narrative way.

Response: Thank you for pointing out our mistakes. We have revised it according to the instructions for authors.

2. The English language should be polished – for instance, in the abstract: “And the CSCAP included…”, or on page 7 line 6: “the disease burden of cardiovascular diseases” (repetitions)

Response: Thank you for your correction. We have the manuscript reviewed by native English academic writer for language improvement.

3. Please mention/provide the approval from the ethics committee

Response: We appreciate the reviewer’s kindly reminding. We have added some sentences in the Methods and analysis part as below.

“The study protocol was approved by the ethics committee of Peking University First Hospital.”

4. The study protocol should be registered first on a public platform – please see the instructions for authors

Response: Thanks for the reviewer’s constructive comments. CSCAP project is not a study to access special intervention methods such as novel medications and devices but a project to implement guideline recommendations for improvement of quality of STEMI care by building up integrated regional networks in China. Thus, the whole CSCAP has not been registered because it is not clinical trial defined by ICMJE. Based on your kindly suggestion, we just applied for the registration in clinicaltrial.gov in Jan, 2019. The Trial registration number is NCT03821012.

5. Please make sure that you do not confuse the “Stent for Life” initiative of the European Society of Cardiology with the “Stent – save a Life” term

Response: Thanks for your kindly notice. The organization name used in this manuscript is correct. The Stent – Save a Life Initiative, following the success of the outstanding Stent for Life program which was effective from 2008 to 2016, is active now. China became the member county of The Stent – Save a Life in 2017.

6. What is the scheduled timeline of this project? Please mention the entire duration of the study, as projected, and the time when the outcomes resulting from model implementation will be measured.

Response: We appreciate the reviewer’s constructive comments. This will help readers to clearly understand the contents of this project. CSCAP is a 10-year project containing 3 phases. It was initiated in 2011 and will be completed in 2021. Phase 1 (CSCAP-1) is conducted from 2011 to 2013, Phase 2 (CSCAP-2) is conducted from 2015 to 2018 and Phase 3 (CSCAP-3) is conducted from 2018 to 2021, respectively. Except cross-sectional analysis in CSCAP-1, the circular enrollment–evaluation–improvement method was implemented in both CSCAP-2 and CSCAP-3 phases. We have revised in the manuscript accordingly.

7. How were the 53 tertiary hospitals selected for the study? The authors mention that they were qualified for PPCI, but on what basis? The number of procedures, the experience of the operators? Also, please include the information if these hospitals are able to provide 24/7 pPCI, as this is extremely relevant for general AMI-related mortality.

Response: Thanks for the reviewer’s constructive comments. The qualification of selected 53 tertiary hospitals in CSCAP-1 is based on the national PCI registry data. Moreover, all of these PPCI hospitals are able to provide 24/7 PPCI service. We have modified it in the methods and analysis section as below.

“The qualification of these selected hospitals is based on the numbers of PCI cases and cardiovascular interventionists extracted from the national PCI registry database. Moreover, all of them are able to provide 24/7 PPCI service.”

8. “Routine clinical assessment and treatment” should be precisely presented – PCI? Statins, antiplatelet, etc… (page 11).

Response: We appreciate the reviewer’s constructive comments. Our project focuses on the integrated network construction by optimizing sources and implementing the evidences recommended by current guidelines. Routine clinical assessment and treatment in this manuscript means guideline-direct management such as reperfusion, auxiliary device implementation, elective revascularization, medications, and therapeutic lifestyle change. In details, it includes selecting reperfusion strategy based on different situation, periprocedural pharmacotherapy of platelet inhibition, anticoagulation and therapies to reduce infarct size and microvascular obstruction, elective revascularization, and medications for secondary prevention including dual antiplatelet therapy, Beta-blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, etc.. We have modified it in the methods and analysis section as below.

“The updated guideline-directed management such as reperfusion, auxiliary device implementation, elective revascularization, medications and therapeutic lifestyle change will be implemented during the whole study period.”

9. The ethics and dissemination part is too long and contains un-necessary discussions, instead of ethical and safety considerations. This should be significantly shortened, remaining only the part related to safety and limitations of the study.

Response: We are very sorry for this mistake, and we have revised this part according to the instruction.

10. A similar approach was presented in a study by Orzan et al (Impact of a Preexisting STEMI Network in Improving STEMI Diagnostic and Treatment in the Community after the Introduction of a National Program of Interventional Treatment in Acute Myocardial Infarction, Journal of Cardiovascular Emergencies, 2015; 1:23-28, DOI: 10.1515/jce-2015-0004), showing significant mortality reduction after implementation of a STEMI network. This should be referenced and commented.

Response: Thanks for the reviewer’s constructive comments. We belief experiences from other country will definitely benefit us. Unfortunately, Journal of Cardiovascular Emergencies recommended by reviewer is not in PubMed database. Due to limited information, we failed to cite this reference in our update manuscript.

Reviewer: 2

Reviewer Name: prof. Menko Jan de Boer

Institution and Country: Department of cardiology, Radboud University Medical Center, Nijmegen, The Netherlands

Please state any competing interests or state ‘None declared’: none

Response: We appreciate the positive comments about the manuscript. The information of declaration has been added at the end of the manuscript as following.

“Competing interests None declared.”

Please leave your comments for the authors below

This is a description of collecting data on STEMI prospectively.

No clinical data are presented although the registry started in 2011

Response: We appreciate the reviewer's constructive comments. The main reason is that this study does not complete yet. But unpublished results extracted from CSCAP-1 and CSCAP-2 already provided the clues to optimize the regional network construction. The protocol of CSCAP-1and CSCAP-2 has been introduced in ESC and LUMEN Global Symposium. Results named "Loading dual antiplatelet therapy in Chinese STEMI patients: results from China STEMI Care Project phase 1 (CSCAP-1)" have been accepted as ESC poster in 2018. In addition, there are several manuscripts are prepared for submission such as the baseline description using CSCAP-1 data and the impact of chest pain center on the improvement of in-hospital outcome including both process and MACE.

Reviewer: 3

Reviewer Name: Edward Koifman

Institution and Country: Soroka University Medical Center, Israel

Please state any competing interests or state 'None declared': None declared

Response: We appreciate the positive comments about the manuscript. The information of declaration has been added at the end of the manuscript as following.

"Competing interests None declared."

Please leave your comments for the authors below

The authors present a study protocol of STEMI network in China. The subject is interesting and deserves attention, and data derived from this registry could impact the health care in China and other places.

To my understanding the study is still ongoing, as such I would suggest to authors to provide the number of patients they plan to enroll in each phase and verify that this will enable them to have enough statistical power to reach solid conclusions regarding treatment interventions.

Response: Thank you very much for the constructive advices. CSCAP focuses a guideline-directed quality of care improvement but not a clinical trial to access a special intervention. Hence, it is not need to calculate the sample size at initial since these treatments are already proved. The study is still ongoing and the first 2 phases have finished patient enrolment with 4,191 patients in CSCAP-1 and 20,799 patients in CSCAP-2, respectively. The estimated patient enrolled number is over 25,000 in CSCAP-3. These numbers are much large than those of previous studies in China such as China-PEACE (~13,000) [1], and thus should have enough statistical power to reach solid conclusions for the network optimization and guideline implementation.

Reference

1. Li J, Li X, Wang Q, Hu S, Wang Y, Masoudi FA, Spertus JA, Krumholz HM, Jiang L; China PEACE Collaborative Group. ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): a retrospective analysis of hospital data. Lancet. 2015;385(9966):441-51.

Also, it is not clear enough what is the medical insurance system in China, how it affects care, and whether it is collected in the database.

Response: Economic burden is a problem in STEMI care in China. There are several types of medical insurances in China. Rural and Urban Residents Medical Insurance, Urban Employees Medical Insurance, and Socialized Medicine Insurance are the 3 major types with different reimbursement ratio. Thus, it should have impacts on the treatment selection in STEMI management. In this study, we designed to collect these information plus in-hospital expense for the purpose of health economics evaluation as well. We have revised it in the manuscript accordingly.

VERSION 2 – REVIEW

REVIEWER	Theodora Benedek University of Medicine, Pharmacy, Science and Technology of Tirgu Mures, Romania
REVIEW RETURNED	24-Feb-2019

GENERAL COMMENTS	The authors succeeded to answer all the reviewer`s comments and suggestions. The article can be published in its current form, representing a complex description of a new networking protocol in STEMI patients, targeting a very large population. The results of this study could add new insights into the current knowledge of STEMI management.

REVIEWER	Edward Koifman Soroka University Medical Center, Israel
REVIEW RETURNED	18-Feb-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 3

Reviewer Name: Edward Koifman

Institution and Country: Soroka University Medical Center, Israel

Please state any competing interests or state ‘None declared’: None declared

Response: Thank you for your advices. We had revised it accordingly.

Please leave your comments for the authors below

No further comments

Reviewer: 1

Reviewer Name: Theodora Benedek

Institution and Country: University of Medicine, Pharmacy, Science and Technology of Tirgu Mures, Romania

Please state any competing interests or state ‘None declared’: none declared

Response: Thank you for your advices. We had revised it accordingly.

Please leave your comments for the authors below

The authors succeeded to answer all the reviewer`s comments and suggestions. The article can be published in its current form, representing a complex description of a new networking protocol in STEMI patients, targeting a very large population. The results of this study could add new insights into the current knowledge of STEMI management