PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical characteristics, managements, and 1-year outcomes of patients with acute coronary syndrome in Iran: The Iranian Project for Assessment of Coronary Events 2 (IPACE2)
AUTHORS	Kassaian, Seyed Ebrahim; Masoudkabir, Farzad; Sezavar, Hashem; Mohammadi, Mohammad; Pourmoghaddas, Ali; Kojouri, Javad; Ghaffari, Samad; Sanaati, Hamidreza; Alaeddini, Farshid; Pourmirza, Behin; Mir, Elham

VERSION 1 - REVIEW

REVIEWER	Przemysław Trzeciak 3rd Department of Cardiology Silesian Center for Heart Diseses, Zabrze, Poland
REVIEW RETURNED	16-Jul-2015

GENERAL COMMENTS	The paper concerns important issue of acute coronary syndromes in Iran. The article cleraly and in details presents epidemiology and treatment of CAS in this part of the world. I appreciate the outcomes of ACS treatment in Iran in spite of economic restrictions. I recommend to publish the paper in BMJ.

REVIEWER	Jose Lopez-Sendon Cardiology Department Hospital Universitario La Paz. La paz Research Institute (IdiPaz) Madrid Spain
REVIEW RETURNED	25-Aug-2015

GENERAL COMMENTS	The authors should be congratulated for organizing and conducting a prospective multicenter registry and offer the data to the scientific community, from a country with little information related to cardiovascular disease diagnostic and therapeutic strategies However, there are several limitations that should be considered and some additional data from the registry should be included in the manuscript - The data refers to a single country. This somehow limits the interest of the potential readers of this journal - The nature of the registry (selected hospitals and number of patients included) do not represent the standard of care a country with about 8o mill inhabitants. The registry is not population based and the number of patients is too small. Probably, patients recruited in each hospital over 17 months were just a fraction of the patients admitted with an acute coronary syndrome. How were the hospitals

	selected? What is the average population covered by the hospitals? How where the patients selected?. If all patients with ACS admitted to the hospitals were included, the incidence of ACS would much lower that in other countries around the world, or the diagnosis was missed or a significant number of patients do not go to the hospital. This is the same critic to the data in many other registries, including some ESC registries, but we can not conclude that the date represents the reality of a country, just the standard of care in a particular group of hospitals. - Where differences found between the hospitals? (mortality, treatments?) - The proportion of patients with unstable angina is very high. This does not reflect the reality in a time when high sensitivity troponinins are commonly used. Data from this group should be described as a separate group, different from STEMI and NonSTEMI. - Patients that died in hospital should not be excluded form the statistical analysis. That is a bias that is not aceptable - Heart failure, along with age, is the most powerful determinant of outcomes. Should be described in more detail (e.g.:Killip class in the 3 different groups (STEMI, NonSTEMI and Unstable angina) - Treatments compare well with standards in western european countries, but the proportion of patients with primary PCI is much lower - There is no excuse to avoid presenting the data on hospital mortality

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Przemysław Trzeciak
Institution and Country 3rd Department of Cardiology
Silesian Center for Heart Diseases, Zabrze, Poland
Please state any competing interests or state ‘None declared’: non declared

Please leave your comments for the authors below
The paper concerns important issue of acute coronary syndromes in Iran. The article clearly and in details presents epidemiology and treatment of CAS in this part of the world. I appreciate the outcomes of ACS treatment in Iran in spite of economic restrictions.
I recommend to publish the paper in BMJ.

Reviewer: 2
Reviewer Name Jose Lopez-Sendon
Institution and Country Cardiology Department
Hospital Universitario La Paz. La paz Research Institute (IdiPaz)
Madrid
Spain
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below
The authors should be congratulated for organizing and conducting a prospective multicenter registry and offer the data to the scientific community, from a country with little information related to cardiovascular disease diagnostic and therapeutic strategies
However, there are several limitations that should be considered and some additional data from the registry should be included in the manuscript

- The data refers to a single country. This somehow limits the interest of the potential readers of this journal
- The nature of the registry (selected hospitals and number of patients included) do not represent the standard of care a country with about 8o mill inhabitants. The registry is not population based and the number of patients is too small. Probably, patients recruited in each hospital over 17 months were just a fraction of the patients admitted with an acute coronary syndrome. How were the hospitals selected? What is the average population covered by the hospitals? How where the patients selected? If all patients with ACS admitted to the hospitals were included, the incidence of ACS would much lower than in other countries around the world, or the diagnosis was missed or a significant number of patients do not go to the hospital. This is the same critic to the data in many other registries, including some ESC registries, but we cannot conclude that the date represents the reality of a country, just the standard of care in a particular group of hospitals.

At first we would like to give our sincere thanks for the honorable reviewer for his brightening and constructive comments. We are completely in agreement with the honorable reviewer that as our study is not population-based our findings are not fully-representative of the management and outcome of the ACS patients in Iran. Accordingly, we regarded this point in limitations section of the manuscript. However, we tried to minimize this bias through collecting data from multiple centers in 5 major provinces of Iran (in North, South, West, East and Central part of Iran).

We recruited the patients consecutively in all hospitals. The first patient was enrolled on April 2011 and the last patient was enrolled on November 2011 and the patients were followed up for 12 months. Hence, the case recruitment period was about 7 months. As we mentioned previously our study is not a nation-wide registry that covers all ACS patients in Iran and the incidence rate of ACS cannot be estimated from our data.

- Where differences found between the hospitals? (Mortality, treatments?)

At first we would like to thank the honorable reviewer for his valuable comments again. Actually for making more sense both for cardiologist and health policy makers, we are working on another manuscript to compare the in-hospital managements and post-discharge outcomes of the ACS patients managed in specialized cardiovascular centers with those managed in general hospitals. We had 6 specialized cardiovascular centers and 5 general hospitals. Below you can find the results of comparison between specialized and general hospitals regarding in-hospital management and post-discharge outcomes. As you can see in the tables, general hospitals are more likely than specialized centers to use LMWH as anticoagulant therapy. Of interest, reperfusion therapy for STEMI patients is more frequently done in general hospitals than specialized centers which might be due to easier and sooner accessibility to general hospitals which makes it more likely to visit the STEMI patient in the golden time for reperfusion. However, as anticipated, the contribution of primary PCI for reperfusion of STEMI patients were significantly higher in specialized cardiovascular centers. The specialized centers were also more likely to perform coronary angiography and to choose invasive (vs. conservative) strategy in management of ACS patients. In addition, the 1-year post-discharge outcome of patients managed in specialized centers were significantly better than those managed in general hospitals in regard to MACE, ACS, and CVA. The protective effect of management in specialized cardiovascular center on 1-year post-discharge MACCE was still present (OR: 0.421, 95% CI: 0.314 – 0.564, P < 0.0001) even after adjustment for Age, Sex, DM, HTN, HLP, Smoking, Family history of CAD, STEMI/new LBBB (vs NSTE-ACS), revascularization (PCI or CABG during index hospitalization), and EF< 40%. In the case that honorable reviewer request, we can add these data to manuscript.

Comparison of clinical characteristics and in-hospital managements of patients managed in specialized cardiovascular centers and general hospitals

Characteristics	Total (n = 1799)	Specialized Cardiovascular center (n = 1330)	General hospital (n=469)	P-value
Male Sex	1177 (65.4)	875 (65.8)	302 (64.4)	0.610
STEMI/NSTE-ACS	463/1336	316/1014	147/322	0.003

Medications, n (%)
Aspirin 1773 (98.6) 1306 (98.2) 467 (99.6) 0.040
Clopidogrel 1652 (91.8) 1230 (92.5) 422 (90.0) 0.096
Dual-antiplatelet therapy 1640 (91.2) 1218 (91.6) 422 (90.0) 0.299
Unfractionated heparin (UFH) 864 (48.0) 730 (54.9) 134 (28.6) <0.0001
LMWH 817 (45.4) 505 (38.0) 312 (66.5) <0.0001
Statin 1697 (94.3) 1255 (94.4) 442 (94.2) 0.908
Beta-blocker 1606 (89.3) 1196 (89.9) 410 (87.4) 0.140
ACEI/ARB 1473 (81.9) 1088 (81.8) 385 (82.1) 0.944
Nitrates 1653 (91.9) 1220 (91.7) 433 (92.3) 0.768
PPIs 746 (41.5) 500 (37.6) 246 (52.5) <0.0001
Reperfusion for STEMI 288 (67.3) 186 (63.2) 102 (76.1) <0.0001
Primary PCI for STEMI 79 (17.3) 66 (22.4%) 13 (9.4%) <0.0001
Invasive strategy 633 (35.2) 533 (40.1) 100 (21.3) <0.0001
At discharge DAPT prescription 1254 (69.7) 924 (69.5) 330 (70.4) 0.770
All plus-minus values are mean ± SD. LMWH, low molecular weight heparin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PPI, proton-pump inhibitor; DAPT, dual-antiplatelet therapy.

Comparison of one-year post-discharge outcomes of the patients managed in general hospital vs. specialized cardiovascular centers
Characteristics Total (n = 1640) Specialized Cardiovascular center
(n = 1330) General hospital (n=469) P-value
Mortality 70 (4.3) 22 (5.2) 48 (3.9) 0.267
Acute coronary syndrome 156 (9.5) 87 (6.5) 69 (14.7) <0.0001
Congestive heart failure 54 (3.3) 12 (2.8) 42 (3.4) 0.551
Stroke/TIA 20 (1.2) 11 (0.9) 9 (2.1) 0.074
MACCE * 246 (15.0) 145 (10.9) 101 (21.5) <0.0001
CABG, coronary artery bypass grafting surgery; PCI, percutaneous coronary intervention.
* Major adverse cardiovascular event including stroke/transient ischemic attack, acute coronary syndrome, and mortality.

- The proportion of patients with unstable angina is very high. This does not reflect the reality in a time when high sensitivity troponins are commonly used. Data from this group should be described as a separate group, different from STEMI and NonSTEMI.
The reason for merging the data of patients with high-risk unstable angina (HR-UA) and NSTEMI in our article were twofold: Firstly, because of the similar pathophysiologic, clinical and angiographic characteristics of HR-UA and NSTEMI current international guidelines for ACS and medical literature are putting both HR-UA and NSTEMI under the single category of NSTE-ACS and we merged them to make our results more comparable to previous studies. Secondly, before merging HR-UA and NSTEMI patients we performed a preliminary analysis on clinical characteristics and managements of the patients with HR-UA and NSTEMI in our study and we observed no significant differences between the two groups. However, in the case that the honorable reviewer still needs separate data for HR-UA and NSTEMI, we are ready to report it separately.
- Patients that died in hospital should not be excluded from the statistical analysis. That is a bias that is not acceptable.
We appreciate the constructive comment of the honorable reviewer. It should be mentioned that the main objective of the current article is to assess 1-year post-discharge outcome of the ACS patients in Iran. Because of the objective of the study that addresses POST-DISCHARGE OUTCOME, excluding patients with in-hospital mortality is unavoidable and we believe that it will not result in any bias. Meanwhile, the in-hospital outcome is the objective of another manuscript which has been scheduled for writing and publication in future.

- Heart failure, along with age, is the most powerful determinant of outcomes. Should be described in more detail (e.g.: Killip class in the 3 different groups (STEMI, NonSTEMI and Unstable angina)
Thanks a lot for your nice suggestion. Actually because our study was a real-world registry-based study and there is evidence that determining the Killip Class has significant inter-observer variability and may cause observer bias we did not assess the Killip class in IPACE2.

- Treatments compare well with standards in western European countries, but the proportion of patients with primary PCI is much lower.
Yes exactly. Unfortunately the contribution of primary PCI in management of STEMI patients in Iran is still much lower than developed countries. Based on the findings of IPACE2 study, Ministry of Health of Iran has just started to maximize the contribution of primary PCI in management of STEMI patients through encouraging and rewarding the PCI-capable centers to run 24/7 primary PCI services.

- There is no excuse to avoid presenting the data on hospital mortality.
As described previously, because of the objective of the study that addresses 1-yer POST-DISCHARGE OUTCOME of ACS patients in Iran, excluding patients with in-hospital mortality is unavoidable and we believe that it will not result in any bias. Meanwhile, the in-hospital outcome is the objective of another manuscript which has been scheduled for writing and publication in future.

VERSION 2 – REVIEW

REVIEWER	Jose Lopez-Sendon Hospital Universitario La Paz Madrid Spain
REVIEW RETURNED	26-Oct-2015

GENERAL COMMENTS	The authors answered all the critics in my previous review. But (all) the limitations remain. The study was presented at the ECC London meeting some weeks ago and was well accepted My concern is the priority for publication in the journal. That is the sole responsibility of the editor

Correction

Kassaian SE, Masoudkabir F, Sezavar H, *et al*. Clinical characteristics, management and 1-year outcomes of patients with acute coronary syndrome in Iran: the Iranian Project for Assessment of Coronary Events 2 (IPACE2). *BMJ Open* 2015;5:e007786.

The institutional affiliation of Dr Ali Pourmoghaddas should be: Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran. In addition, the first name of the co-author Bahin Pourmirza is misspelt and should be 'Behin'.

BMJ Open 2016;**6**:e007786corr1. doi:10.1136/bmjopen-2015-007786corr1

Correction

Kassaian SE, Masoudkabir F, Sezavar H, *et al*. Clinical characteristics, management and 1-year outcomes of patients with acute coronary syndrome in Iran: the Iranian Project for Assessment of Coronary Events 2 (IPACE2). *BMJ Open* 2015;5:e007786. There is a misspelling of the sixth author's name in this paper. The author's correct name is Javad Kojuri.

BMJ Open 2016;**6**:007786corr2. doi:10.1136/bmjopen-2015-007786corr2