PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Exploration into lipid management and persistent risk in patients hospitalised for acute coronary syndrome in Japan (EXPLORE-J): Protocol for a prospective observational study
AUTHORS	Nakamura, Masato; Uno, Kiyoko; Hirayama, Atsushi; Ako, Junya; Nohara, Atsushi; Arai, Hidenori; Harada-Shiba, Mariko

VERSION 1 - REVIEW

REVIEWER	Kevin Selby Kaiser Permanente Division of Research, Oakland, CA, USA Department of Ambulatory Care and Community Medicine, University of Lausanne, Switzerland
REVIEW RETURNED	04-Nov-2016

GENERAL COMMENTS	The topic of study is important and is adequately addressed using a prospective cohort of patients after ACS. My main concerns are not with the limitations mentioned by the authors (observational nature and small sample size). Rather, I am concerned by the lack of clarity of the introduction / aims, and problems with possible sampling bias not that are not addressed. First, with regard to the introduction and aims. The authors state that the primary objective is to follow major CV events in survivors of acute coronary syndrome, with a specific focus on the roles of familial hypercholesterolemia, LDL cholesterol, statin treatment, and PCSK-9 gene status. If this is true, several point should be clear throughout: - all conclusions will be with regards to secondary prevention and ACS survivors. The authors talk extensively about primary prevention treatment thresholds and the prevalence of FH in the general population. For example, is Figure 1 relevant? They will not be able to answer questions about primary prevention and the general population. - In this population at known high risk and with extensive proof of the need for secondary prevention with statins, it seems difficult to address questions about treatment thresholds for FH. Is this an appropriate focus? - Similarly, in people with known CVD and known high risk, I have trouble seeing how PCSK9 gene status will be important. Please clarify for me how that test could change management and be helpful. The second concern I have is about possible selection bias. The authors mention that they have 59 sites that contributed consecutive patients between April 2015 and August 2016,and there are 2,016 patients? That's only 34 patients per site, which seems very low. Especially if all patients with NSTEMI and unstable angina were also included. Please give more detail about efforts to enroll ALL

	hospitalized patients with these syndromes at ALL 59 sites, and how difficulty doing so could bias results. Further, please mention the difficulties with ensuring the diagnosis of all NSTEMI and unstable angina patients and how inclusion of these patients could also bias results. Finally, very little information is provided about how to ensure complete follow-up for this large, multi-centric cohort. Please specify what efforts will be made to prevent, and if needed account for loss to follow-up.

REVIEWER	Paolo Magni Universita' degli Studi di Milano Milano Italy
REVIEW RETURNED	19-Jan-2017

GENERAL COMMENTS	The paper by Nakamura et al. reports the rationale and design of an interesting multicentre, prospective, observational (registry) study aimed at evaluating the several aspects of lipid management and cardiovascular risk in Japanese patients with acute coronary syndrome, including the assessment of the prevalence of familial hypercholesterolemia in this cohort as well as of the PCSK9 levels in these patients. Overall, the paper reads clearly and the design is satisfactorily described. Importantly, the trial has been registered. I have, however, some specific comments: Page 6, line 32 Some references need to be updated and extended. For example, in the Introduction the Japanese guidelines for the prevention of atherosclerosis (2012) are mentioned. I suggest to add also more recent guidelines, including the 2016 EAS/ESC guidelines (Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016 Oct 14;37(39):2999-3058). Page 8, line 30 The ODYSSEY trial is mentioned: please update this information with more recent reports from this and other studies (OSLER and ODYSSEY LONG TERM). Page 9, table 1 and text How FH is diagnosed? Along with the reported criteria, maybe it is important to report also the Dutch Lipid Clinic Network (DLCN) criteria (Nordestgaard BG, Chapman JM, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. European Heart Journal 2013; 34:3478-3490 Page 17, line 52 PCSK9 concentrations: please check whether the mean or the median is better, according to the normality distribution of the data.

	A radiography of the Achilles tendon is mentioned: is it correct? Is it better to perform a sonographic evaluation of this tendon thickness?

VERSION 1 – AUTHOR RESPONSE

Responses to the comments of Reviewer #1:

The topic of study is important and is adequately addressed using a prospective cohort of patients after ACS. My main concerns are not with the limitations mentioned by the authors (observational nature and small sample size). Rather, I am concerned by the lack of clarity of the introduction / aims, and problems with possible sampling bias not that are not addressed.

First, with regard to the introduction and aims. The authors state that the primary objective is to follow major CV events in survivors of acute coronary syndrome, with a specific focus on the roles of familial hypercholesterolemia, LDL cholesterol, statin treatment, and PCSK-9 gene status.

If this is true, several point should be clear throughout:
- all conclusions will be with regards to secondary prevention and ACS survivors. The authors talk extensively about primary prevention treatment thresholds and the prevalence of FH in the general population. For example, is Figure 1 relevant? They will not be able to answer questions about primary prevention and the general population.

Response: In accordance with this comment, we have deleted Figure 1.

- In this population at known high risk and with extensive proof of the need for secondary prevention with statins, it seems difficult to address questions about treatment thresholds for FH. Is this an appropriate focus?

Response: FH is one of the highest, independent, pharmacologically modifiable risk factors of coronary artery disease including ACS. We believe that this disease deserves specific attention because of the higher risk of recurrence after ACS; thus, there is a potential need for more intensive lipid lowering strategies. This registry will probably not define the threshold LDL-C level for secondary prevention in FH patients. However, diagnosing FH in this population and comparing FH patients with non-FH patients in terms of their outcomes in clinical practice may provide some insight.

- Similarly, in people with known CVD and known high risk, I have trouble seeing how PCSK9 gene status will be important. Please clarify for me how that test could change management and be helpful.

Response: FH is largely clinically diagnosed; however, the diagnosis may not be obvious because of statin use or low LDL-C level immediately following ACS. Furthermore, some patients may not have clinical FH. However, it is known that having genetic mutations consistent with FH is an independent risk factor for developing coronary artery diseases. Guidelines recommend a lower LDL-C target in FH patients (e.g., the European Society of Cardiology target LDL-C is lower in patients with coronary artery disease and FH than in patients with coronary artery disease alone). Thus, we believe it is important to seek genetic information for FH in an effort to improve the diagnosis of FH in high-risk patients.

The second concern I have is about possible selection bias. The authors mention that they have 59 sites that contributed consecutive patients between April 2015 and August 2016, and there are 2,016 patients? That's only 34 patients per site, which seems very low. Especially if all patients with NSTEMI and unstable angina were also included. Please give more detail about efforts to enroll ALL hospitalized patients with these syndromes at ALL 59 sites, and how difficulty doing so could bias

results. Further, please mention the difficulties with ensuring the diagnosis of all NSTEMI and unstable angina patients and how inclusion of these patients could also bias results. Finally, very little information is provided about how to ensure complete follow-up for this large, multi-centric cohort. Please specify what efforts will be made to prevent, and if needed account for loss to follow-up.

Response: We believe that the registration of successive patients (as in our study) would restrict biases concerning the selection of patients. The main reason for the low number of patients is the low number of ACS patients per facility in general. Another reason is that patients who had been enrolled in interventional clinical trials were not eligible to be registered in this observational study. However, the number of patients included in this study per site is the norm for Japanese facilities. For example, the average number of ACS patients treated in 2011 in private university hospitals, public university hospitals, national public hospitals, and general hospitals was approximately 90, 55, 90, and 38, respectively.

There were no difficulties in enrolling patients from the 59 sites. The enrolment of patients was as expected, with some seasonal variations, and there were no difficulties in ensuring the diagnoses of all NSTEMI and UA patients.

Clinical research coordinators as well as the participating physicians will be involved in ensuring the follow-up of this large multicentric cohort. Letters will be sent to the patients/facilities in cases involving hospital/clinic transfers.

Responses to the comments of Reviewer #2:

The paper by Nakamura et al. reports the rationale and design of an interesting multicentre, prospective, observational (registry) study aimed at evaluating the several aspects of lipid management and cardiovascular risk in Japanese patients with acute coronary syndrome, including the assessment of the prevalence of familial hypercholesterolemia in this cohort as well as of the PCSK9 levels in these patients. Overall, the paper reads clearly and the design is satisfactorily described. Importantly, the trial has been registered.

I have, however, some specific comments:

Page 6, line 32
Some references need to be updated and extended. For example, in the Introduction the Japanese guidelines for the prevention of atherosclerosis (2012) are mentioned. I suggest to add also more recent guidelines, including the 2016 EAS/ESC guidelines (Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016 Oct 14;37(39):2999-3058).

Response: The updated reference has been added to the revised manuscript.

Page 8, line 30
The ODYSSEY trial is mentioned: please update this information with more recent reports from this and other studies (OSLER and ODYSSEY LONG TERM).

Response: The ODYSSEY trial is still the largest “outcome trial” using PCSK9 inhibitor, alirocumab. OSLER and ODYSSEY LONG TERM evaluated the long-term efficacy and safety of PCSK9 inhibitors, but it is not designed to evaluate the outcomes.Explore-J does not specifically evaluate the effect of PCSK9 inhibitors, thus this sentence was removed from the revised manuscript.

Page 9, table 1 and text
How FH is diagnosed? Along with the reported criteria, maybe it is important to report also the Dutch Lipid Clinic Network (DLCN) criteria (Nordestgaard BG, Chapman JM, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. European Heart Journal 2013; 34:3478-3490

Response: In our study, FH was diagnosed based on the Japan Atherosclerosis Society criteria, which has been evaluated in the Japanese population (Table 1). We are considering using the DLCN criteria for comparison purposes; however, obtaining all the data to implement the DLCN criteria is not feasible in our study design, and thus the data will be limited.

Page 17, line 52
PCSK9 concentrations: please check whether the mean or the median is better, according to the normality distribution of the data.

Response: Thank you for pointing this out. We have reviewed this internally, and agree that the median is a more appropriate summary statistic to report for these data.

A radiography of the Achilles tendon is mentioned: is it correct? Is it better to perform a sonographic evaluation of this tendon thickness?

Response: Some studies have reported better sensitivity and specificity with ultrasonographic evaluation of the Achilles tendon. However, radiographic evaluation is the only validated method in Japan and is recommended by the Japan Atherosclerosis Society FH guidelines (J Atheroscler Thromb 2012;19:1019–26).

VERSION 2 – REVIEW

REVIEWER	Kevin Selby University of Lausanne, Switzerland
REVIEW RETURNED	15-Mar-2017

GENERAL COMMENTS	I feel that the authors have adequately addressed the reviewer comments. I was primarily concerned that: i) they claimed to be examining primary prevention, which they removed; ii) they are not capturing all ACS cases at the included hospitals, and the authors insist that they are.

REVIEWER	Paolo Magni Universita' degli Studi di Milano, Milano, Italy
REVIEW RETURNED	25-Mar-2017

GENERAL COMMENTS	The Authors responded to all queries.