Author's response to reviews

Title: Early decrease in carotid plaque lipid content as assessed by magnetic resonance imaging during treatment of rosuvastatin

Authors:

Rui-Xue Du (drx1972@hotmail.com)
Jian-Ming Cai (beili12345@sina.cn)
Xue-Qiao Zhao (xzhao@cardiology.washington.edu)
Qing-Jun Wang (wangqingjun77@163.com)
Dan-Qing Liu (ldq562892650@126.com)
Wen-Xiu Leng (lenslin301hosp@yahoo.com)
Peng Gao (jiandangaop@126.com)
Hong-Mei Wu (wuhtm301@sina.com)
Ping Ye (yeping@sina.com)
Lin Ma (cjr.malin@vip.163.com)

Version: 4 Date: 11 June 2014

Author's response to reviews: see over
Dear Editor and Reviewer,

Thank you for your letter and for the Reviewer’s advice concerning our manuscript entitled “Rapid decrease in carotid plaque lipid content as assessed by magnetic resonance imaging during treatment of rosuvastatin” (MS: 3718907361190142). We have revised the paper again, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in blue in the revised manuscript. The main corrections in the paper and the responds to the Reviewer’s comments are as following:

**Response to comment:**

1. MRI analysis of plaque composition: Despite the authors described that the lipid-rich necrotic core (LRNC) was identified by using multicontrast weightings plus post-contrast T1W images, it is still hard for readers to image how to decide LRNC once there are discrepancies among different MRI-weighted images. Therefore, a hierarchical algorithm for the MRI analysis of LRNC should be provided (Yuan C, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. Circulation 2001;104:2051-6.).

2. Figure 3. According to the MRI diagnostic criteria of LRNC as stated in this manuscript and the above-cited reference (Yuan C, et al. Circulation 2001;104:2051-2056.), the selected lipid content was obviously overestimated since LRNC should be hypointense in T2W. However, the yellow circle included hyperintense area in T2W. This discrepancy again reflects the importance of the hierarchical algorithm for identification of LRNC. The authors should redraw the selected lipid content in Figure 3. The abbreviation CETIW should be detailed as well.

**Response:**

Thank you for the comments. It is necessary to provide the hierarchical
algorithm, which is helpful for readers to understand how to decide LRNC. Otherwise, there are some limitations concerning the hierarchy in Yuan’s article (published in 2001).

1) Although Yuan’ group found that many of the necrotic core regions appeared hypointense on T2W imaging; they also found that the LRNC in other regions was isointense on T2W images. One explanation for the discrepancy is that the population of patients and complexity of lesions examined differs from those studied in previous reports (see Yuan’s article, page 2055).

Furthermore, it was found that LRNC also present hyperintense on T2W images in later studies (Rikin A. Trivedi, et al. MRI-derived measurements of fibrous-cap and lipid-core thickness: the potential for identifying vulnerable carotid plaques in vivo. Neuroradiology 2004; 46:738-743). Thus, LRNC has varied signal intensity on T2W images including hypointense, isointense, and hyperintense. The capability of T2W imaging to identify LRNC is weak.

2) More importantly, LRNC can only be identified rather than be quantified accurately according to Yuan’s method in 2001. In 2005, the same group suggested a new algorithm in Cai’s article using contrast enhanced T1-weighted imaging, which has the capability to delineate LRNC boundaries. (Cai, et al. In vivo quantitative measurement of intact fibrous cap and lipid rich necrotic core size in atherosclerotic carotid plaque: a comparison of high resolution contrast enhanced MRI and histology. Circulation 2005, 112:3437-3444.) The new algorithm, by combining multiple weightings, particularly contrast enhanced T1-weighted imaging, provided an accurate and reproducible means to quantify plaque components including LRNC.

According to Cai’s algorithm, LRNC demonstrate isointense to hyperintense on precontrast T1W images and TOF. With the noncontrast T1W image as a baseline for comparison, the LRNC area was identified on the postcontrast T1W image as the area with no or slight contrast enhancement compared with the surrounding, more strongly enhanced fibrous tissues.

The LRNC areas measured by above method and histology were strongly correlated (r = 0.84, P < 0.001) and was widely accepted as a viable tool for LRNC
quantification and has been used in our and other studies.

Therefore, the selected lipid content was not overestimated in Fig.3. We have added corresponding reference in the Method part and corrected some sentences in Figure legends (Figure 3).

The abbreviation CETIW was detailed as contrast enhanced T1-weighted.

3. Given that there were no statistically significant differences in LRNC measured at 3 months, 12 months, and 24 months, it would be not appropriate to state that “LRNC volume and %LRNC continued to decrease moderately at 12 and 24 months”. It should be interpreted as no further decrease in LRNC volume or %LRNC after 3 months. Please revise or provide reasonable explanations.

Response:

We have rewritten this part according to the Reviewer’s suggestion:

“LRNC volume and %LRNC continued to decrease moderately at 12 and 24 months, although this trend was not significant.”

Minor Essential Revisions

1. Natural course of LRNC: According to the references cited by the authors (8, 9, 31, 32), we cannot find evidence showing that LRNC would generally become larger in the future. In the ESTABLISH trial, the coronary plaque volume (rather than LRNC) increased gradually in the usual care group. However, there are no previous studies reporting that the LRNC would increase in size. Please clarify.

Response:

It is really true as Reviewer suggested that there are no previous studies reporting that the LRNC would increase in size. We have made correction according to the Reviewer’s comments in Discussion part.

“And we cannot exclude the possibility that LRNC may turn into fibrosis in months as a natural process. However, most previous investigations indicated that plaque seemed prone to progress rather than regress without lipid-lowering therapy
[31, 32], and LRNC was usually regard as one of the important factors leading to plaque increase.”

2. Title: The word “rapid” may be too strong for the findings. “Early decrease” looks more neutral. Please revise.

Response:

We have made correction according to the Reviewer’s comments.

Others

Needs some language corrections before being published

Response: The revision has been edited by native English-speaking experts.

Special thanks to you for your good comments. We hope that the revision is acceptable, and I look forward to hearing from you soon.

Yours sincerely,

Ping Ye, MD.