Author's response to reviews

Title: Assessment of Plaque Evolution in Coronary Bifurcations Located Beyond Everolimus Eluting Scaffolds: Serial Intravascular Ultrasound Virtual Histology Study

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Response to the Reviewers

Reviewer 1: Dr. Kenichi Tsujita

(General comments from the reviewer)

The paper by Lee et al. describes an interesting study that examined the atherosclerotic evolution in coronary bifurcations located proximally and distally to a bioresorbable vascular scaffold (BVS) with the use of intravascular ultrasound (IVUS). When examining separately the bifurcations located proximally and distally to the BVS, no changes were found at the distal bifurcations, while at the proximal bifurcations there was a statistical significant decrease in the plaque burden (36.67±13.33% at baseline vs. 35.06±13.20% at 2 years follow-up, p=0.04). Taken these findings into consideration, the authors speculated that the results may potentially be due to the effect of the downstream drug delivery on vessel wall physiology. Although these IVUS findings are of potential interest, additional discussion is strongly recommended to promote our better understanding of the atherosclerotic evolution in coronary bifurcations.

We thank the reviewer for the constructive comment. In the original manuscript we have devoted a paragraph (the 3rd paragraph) describing the evidence from intravascular imaging studies assessing plaque morphology and evolution in bifurcation lesions. To address the reviewer comment we have added two more sentences in the revised draft that present the findings of the largest to our knowledge study that compares plaque morphology and burden between bifurcation-located and non-bifurcation located lesions: “It is well known that bifurcation anatomies are prone to atherosclerosis; and recently we have showed that the lesions located at the bifurcation site have an increased atheroma burden and lipid component compared to the lesions located in a non-bifurcated segment [21]. The differences in the plaque composition and burden between bifurcation and non-bifurcation lesions should at least partially be attributed to the complex flow patterns seen in these segments.”

(Specific comment from the reviewer)
In each bifurcation, the frames portraying the proximal rim, in-bifurcation, and distal rim of the ostium of the side branch were analyzed. The geometric parameters and plaque types were then evaluated at baseline and 2-years follow-up. However, there were no significant differences in the geometrical parameters such as lumen, vessel and plaque areas as well as in the composition of the atheroma between baseline and 2-years follow-up. Underlying this negative data, there may be methodological problem. As the authors described in the Discussion section, at the distal rim of the ostium of the side branch and in particular at the outer side of the flow divider low or oscillating shear stress have been detected and these segments appear to be susceptible to atherosclerosis, in-depth analysis (e.g. IVUS image acquisition both from main branch and side branch as shown in a paper by Oviedo et al. [Circ Cardiovasc Interv 2010;3;105-112]) was required to elucidate the atherosclerotic evolution in coronary bifurcations. The authors had better mention about the methodological limitation.

We agree with the reviewer’s comments regarding IVUS assessment of plaque evolution in bifurcation lesions. In the present study, we used IVUS to assess changes in the atheroma burden and plaque composition only in the main branch and not in the side branch and this is a limitation of our analysis which has been mentioned in the revised manuscript at the limitation section: “Furthermore, in contrast to previous studies serial IVUS imaging was performed only in the main branch and not in the side branch of the bifurcation lesion. This is a significant limitation of our study since we were not able to evaluate coronary pathology in side branches and detect changes in plaque composition and burden in these segments.”

However it is also likely the aggressive pharmaceutical treatment with statins to have halted atherosclerotic evolution. Besides large scale studies such are the SATURN study and the IBIS II study have shown only minor change in the atheroma volume and the composition of the plaque that were not detected by our small scale study.

(Specific comment from the reviewer)

The authors analyzed separately bifurcations located proximally and distally to the BVS, and found plaque regression at the proximal group and no changes in the plaque at the distal group. They explained that this may potentially be due to the effect of the
downstream drug delivery on vessel wall physiology. In view of the small number of the study patients, the credibility of the results is questioned, and the study itself is hypothesis-generating.

We agree with the reviewer that this is a major limitation of our analysis. We discuss this drawback in the limitation section which now reads: “The most important limitation of this analysis is the small number of the recruited patients and the limited number of the bifurcations studied. Hence this report may be underpowered to detect differences in plaque burden and composition. Thus this study should be considered as an exploratory and hypothesis generating analysis and the results should be interpreted with caution. In view of the limited data we were restricted either to a descriptive report or to a simplified statistic analysis and we did not take into consideration the clustering effect.”

(Specific comment from the reviewer)
*Figure 4 seems to lead misunderstanding to the readers, because serial change of the plaque burden was quite similar between proximal and distal bifurcation. Please remake the graph, and clarify the difference between the groups.*

We agree with the reviewer that the difference in the changes in plaque burden between proximal and distal bifurcation was marginal. This is apparent in figure 4 which actually instead of highlighting the reported difference it actually shows a similar change in the atheroma burden in the proximal and distal bifurcation. Thus following the reviewer comment we have removed figure 4 from the revised draft.

**Reviewer 2: Dr. Meihua Zhu**

(Response to the reviewer)
The authors would like to express sincere appreciation for reviewing our manuscript. We hope our manuscript merits publication providing useful information about change in plaque characteristics beyond the bioresorbable scaffold implantation segment.