Author’s response to reviews

Title: Transcatheter MitraClip Repair Alters Mitral Annular Geometry – Device Induced Annular Remodeling on Three-Dimensional Echocardiography Predicts Therapeutic Response

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Kim et al. / Cardiovascular Ultrasound/ CARU-D-19-00095

Reviewer #1
This study is very interesting as it focalizes for the first time the potential role of the annular geometry changes in predicting the therapeutic response of MitraClip procedure. I think some points deserve to be analyzed:

We thank the Reviewer for a careful reading of our manuscript, and for an array of insightful suggestions that have helped to improve our paper. Detailed below is a detailed point-by-point response to all issues raised.

1. It is not specified if the study design is retrospective or prospective and what kind of clip has been used (NTr or XTr).

We apologize for these omissions. The revised manuscript now clarifies that this study entailed “analysis of pre-existing (retrospective) data” (page 6, lines 10).

Regarding MitraClip type, we note that the large majority (70/80) of patients in our cohort received the MitraClip NT/NTr device, which we believe makes sense given that the study population comprised patients undergoing percutaneous repair between 2013 – 2019 (XTr commercially approved in United States; 2018). The revised manuscript now specifies the following: “MitraClip implantation employed the NTr device type in over three-fourths of cases (87% NT/NTr; 13% XTr)” (page 9, lines 6-7).

In addition, the Discussion section has been expanded to highlight the need for future studies to test whether our findings (including device-induced annular remodeling) vary based on device type:

“Whereas a large majority (70/80) of patients in our study population underwent repair using the MitraClip NT/NTr device, our finding of an impact of MitraClip on annular remodeling is of particular relevance in context of new modifications of the device (XTr) that grasp a wider amount of leaflet tissue and would thus be expected to apply a greater magnitude of force on the mitral annulus. It is also possible that greater magnitude of leaflet grasp would better resist tethering forces exerted by sub-valvular myocardium, and thus provide a more durable reduction of MR. In this context, future studies are warranted to test whether pattern and magnitude of induced annular remodeling are similar irrespective of MitraClip device type, and whether specific types of MitraClip mitigate or augment the impact of device-induced annular remodeling on post-procedure MR” (page 14, lines 6-14).

2. It could be also useful to know if worse results are correlated with the use of more than 1 clip. According to your findings in which a greater geometrical remodeling caused by the device correlates with sub-optimal results, the use of more than one clip should be associated with more severe residual MR.

We appreciate the importance of this issue and have performed additional analyses to address this. Table 1 now reports on number of implanted devices: Results demonstrate that patients with and without MitraClip response (≤ mild MR on follow-up) were similar with respect to number
of clips implanted, irrespective of whether compared based on mean (1.61±0.50 vs. 1.64±0.64, p=0.81) or proportion of patients who received multiple clips (61% vs. 55%, p=0.64).

3. It could be interesting to have some data about the modifications of anterior and posterior leaflets’ angle and non-planar angle.

We thank the Reviewer for this suggestion and have performed additional analyses to address this important issue. Our results (included in our revised manuscript) demonstrate that pre-procedural leaflet angles did not differ between patients with and without optimal MitraClip response (see Tables 3 and 4), and that angular indices did not significantly change when compared immediately pre- and post-procedure on 3D trans-esophageal echo (Table 6).

We believe that these newly included data add to the scope of our manuscript by further highlighting the importance of specific geometric indices impacted by MitraClip: Our findings indicate that stretch effects induced by the device are predominantly planar, as evidenced by device-induced alterations in annular area, circumference, and linear indices (all p<0.001 when compared pre vs. post device implantation).

4. The study population is primarily degenerative and the authors specified that leading pathologies were prolapse, annular calcification and valve thickening. It may be useful to know the specific criteria used for patients' selection: had the Authors included anatomical characteristics beyond the EVEREST criteria known to be associated with less favourable results (complex prolapses, excessive valve thickening or calcifications)?

We appreciate this insightful comment. Our study encompassed consecutive patients undergoing MitraClip who had pre- and post-procedural echo, as we aimed to study a broad population reflective of general clinical practice – no patients were excluded based on imaging, procedural, or clinical characteristics. While it is certainly true that results of EVEREST (or other clinical trials) could have influenced decisions to refer for MitraClip, no patients were excluded from our cohort based on pre-specified criteria that could potentially bias our results. We apologize for any potential uncertainty regarding this issue, and have modified our text so as to better clarify this issue:

“The study population comprised consecutive patients with advanced (≥moderate) MR who underwent MitraClip at Weill Cornell Medicine (NY, NY) in whom intra-procedural TEE was available to evaluate annular geometry, and TTE was performed pre- and post- (1-6 months [target 6 months]) procedure to assess change in MR: No otherwise eligible patients were excluded based on procedural outcomes, imaging findings, or clinical indices” (page 6, lines 2-6).

In addition, Table 2 in the revised manuscript provides a breakdown of mitral valve pathologies - including annular calcification and mitral thickening – which are also tested in relation to MitraClip response (p=NS).

5. It is not specified the acutely post-procedural results about residual MR associated with geometrical annular modifications. This point has relevance in order to know if the sub-optimal
results shown at the follow-up are related to the adverse remodeling caused by the clip over time, as the Authors have speculated, or if it is the consequence of some basal valvular and ventricular anatomical features.

We thank the Reviewer for this comment and appreciate the potential importance of this issue. While all patients in our study underwent implantation of MitraClip and had standardized pre- and post- (1-6 month) transthoracic echo (TTE) to assess therapeutic response, additional (acute) post-procedural TTE was not acquired in a standardized manner immediately post-device implantation: In this context, we do not have a uniform dataset with which to examine time course of MR recurrence so as to elucidate relative contributions of residual MR and device-induced annular remodeling. Accordingly, our revised manuscript now acknowledges this as a study limitation as well as an area for future research in the Discussion section:

“It is also important to recognize that follow-up was performed at a single time point after MitraClip, and that TTE was not performed immediately after device implantation. Accordingly, our analyses were unable to test relative contributions of residual MR and device-induced annular remodeling as determinants of MitraClip response – further studies employing serial imaging and more precise metrics of annular/myocardial stretch are necessary to expand on results of the current study”  (page 16, lines 13-17).

6. The Authors' hypothesis about the unfavourable remodeling directly caused by the clip through the augmented leaflet stress immediately adjacent to the device as well as LV myocardial stretch adjacent to the mitral annulus is not fully sharable. It is indeed in contrast with the recent favourable clinical experience with the use of XTr devices. These devices notoriously grasp a wider amount of leaflet tissue, then applying a greater force on mitral valve apparatus.

As above (see response to issue #1), we note that the large majority (70/80) of patients in our cohort underwent MitraClip using the NT/NTr device, which we believe makes sense given that our study population comprised patients undergoing percutaneous repair between 2013 – 2019 (i.e. XTr commercially approved in United States; 2018). Whereas only a small number of patients in our cohort received the XTr device, exploratory analysis indicates that therapeutic response in our cohort did not markedly vary based on device type, as evidenced by non-significant differences in optimal response (≤mild MR) among patients receiving NT/NTr XTr type devices  (p=0.55).

Irrespective of the above, we would respectfully contend that our findings – regarding impact of MitraClip on annular remodeling – are of particular relevance in context of newly introduced MitraClip design (XTr), which – as noted by the Reviewer, grasps a wider amount of leaflet tissue, and would thus be expected to apply a greater magnitude of force on the mitral annulus. It is also possible that greater magnitude of leaflet grasp would better resist tethering forces exerted by sub-valvular myocardium, and thus provide a more durable reduction of MR (especially in patients with LV dilation and/or fibrosis [conditions in which LV mediated tensile forces on the device are augmented]). Accordingly, our Discussion section has been expanded to highlight the need for future studies to test whether our findings (including device-induced annular remodeling) are similar irrespective of MitraClip device type, and whether specific types of
MitraClip (e.g. XTr) mitigates or augments the impact of device-induced annular remodeling on post-procedure MR:

“Whereas a large majority (70/80) of patients in our study population underwent repair using the MitraClip NT/NTr device, our finding of an impact of MitraClip on annular remodeling is of relevance in context of new modifications of the device (XTr) that grasp a wider amount of leaflet tissue, and would thus be expected to apply a greater magnitude of force on the mitral annulus. It is also possible that greater magnitude of leaflet grasp would better resist tethering forces exerted by sub-valvular myocardium, and thus provide a more durable reduction of MR. In this context, future studies are warranted to test whether pattern and magnitude of induced annular remodeling are similar irrespective of MitraClip device type, and whether specific types of MitraClip mitigate or augment the impact of device-induced annular remodeling on post-procedure MR.” (page 14, lines 6-14).

7. Considering that one of the study aims is to find some pre-procedural anatomical hallmarks in order to predict MitraClip therapeutic response, it could be useful to suggest some cut-offs about LV volume and mitral annular size. An independent predictive role of mitral annular area, annular circumference, anteroposterior diameter for poor response was demonstrated. It would be useful to provide cutoffs of these variables.

We thank the Reviewer for this guidance: As suggested, Table 4 has been substantially expanded to provide potential cutoff values (derived from ROC analyses) for all variables tested in our study (including annular area, circumference, and antero-posterior diameter).

8. In the discussion the authors hypothesize a causal correlation between MitraClip induced alterations on annular geometry and suboptimal result during follow up. These indexes are calculated from basal annular area and circumference, which the authors demonstrated to be independently associated with poor response. Therefore these findings may be incidental and concomitant. In order to establish an independent and causal correlation, the authors should identify on ROC analysis a cutoff of Delta annulus area or delta annulus circumference which can predict poor response as well as to include the variable "Delta annulus area" or "delta annulus circumference" in univariate and multivariate analysis for the prediction of poor response.

We fully appreciate the importance of this issue. We do respectfully note though that our study primarily focused on pre-procedural indices as predictors of recurrent MR, for which additional analyses (detailed above) now provide ROC cutoffs.

Regarding device induced stretch, we respectfully point out that this aspect of our study was intended to elucidate mechanism for recurrent MR, given that prior studies by an array of groups (including our own) have shown LV/annular dilation to predict recurrent MR after MitraClip with uncertainty as to whether the device itself alters annular geometry as well as whether magnitude of such device-induced annular reshaping is greater among patients with sub-optimal MR response to MitraClip. Given that (as noted by the Reviewer) “MitraClip induced alterations on annular geometry … are calculated from basal annular area and circumference”, these indices are intrinsically derived from (i.e. covariate with) with geometric indices, we are unable to
adequately test independent (or incremental) utility of stretch based predictors within our current sample size.

That being said, we greatly appreciate the importance of this issue and have expanded our Discussion section to highlight this as an important priority for future larger scale research:

“Given our sample size (n=80) and the fact that device-induced annular remodeling is intrinsically related to pre-procedural chamber geometry, our analyses were insufficiently powered to test whether baseline LV chamber size and device-induced remodeling were independent predictors of MitraClip response, as well as whether pre-procedural LV geometry, myocardial substrate (fibrosis), and device-induced annular remodeling synergistically impacted MR recurrence after MitraClip. Further, larger scale, research is warranted to test the relative prognostic utility of valvular and annular remodeling indices – inclusive of device-induced changes in annular geometry - as predictors of MitraClip response.” (pages 15-16, lines 21-23 and 1-5).

Of course, if there are any other specific additions to the manuscript that the reviewer feels warranted, we would be happy to add these.

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Reviewer #2

In this very interesting paper, Kim and colleagues present a retrospective series of 80 subjects undergoing MitraClip for moderate to severe (3+ to 4+) mitral regurgitation. In this series they report on the impact of left ventricular and atrial volumes and, most interestingly, mitral annular geometries, on short term response to in terms of MR reduction after MitraClip. The implant of MitraClip on annular geometry was also evaluated. At a mean follow up of 2.5 months, patients with 1+ or less MR were 59% of the total and were the ones with smaller pre-procedural LV and LA sizes as well as annular size dimensions. MitraClip reduced annular dimensions in all subjects, but the magnitude of reduction was greater in those who had an optimal response to the device. The work is interesting, well written and presented. I have some suggestions:

We thank the Reviewer for a careful reading of our manuscript, and for an array of insightful suggestions and that have helped to improve our paper. Detailed below is a detailed point-by-point response to all issues raised.

1. The grading of post-implant residual MR is still a matter of intense debate. Please fully report which parameter have you taken into consideration, and report how many patients have no residual MR, how many 1+, 2+, 3+ and 4+ residual MR. I would also suggest providing a supplementary table in which to indicate the specific values for the parameters taken into consideration (e.g. EROA, RVol…) in responders vs. non responders.
As suggested, we have expanded this aspect of our manuscript, which now reports that:

“MR was graded [by dedicated level III readers] “using consensus guidelines … for which primary components included vena contracta, regurgitant fraction, regurgitant volume, and effective regurgitant orifice area (EROA)” (page 8, lines 6-9)

We recognize that our study employed integrated, semi-quantitative, grading criteria to assess MR rather than a singular isolated criterion. However, respectfully note that our approach is consistent with that applied in prior multicenter studies of MitraClip, for which post-procedural MR severity has been similarly assessed (e.g. Feldman et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST cohort. JACC 2009; 54: 686 | Mauri et al. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for MR. JACC 2013; 62: 317). Our approach is also consistent with methods applied and validated by our group in prior studies of MitraClip (Kim et al. CCI 2019) as well as prior epidemiologic and outcomes research on MR (Jones et al. Am J Cardiol 2001 | Volo et al. Am J Cardiol 2014 | Kampaktsis et al. JAHA 2019), supporting the notion that MR analyses were rigorous and broadly generalizable.

As suggested by the Reviewer, we have expanded our manuscript to provide a breakdown of MR severity as assessed on follow-up:


In addition, our revised manuscript now explicitly acknowledges this issue as a potential study limitation:

“… our study defined optimal MitraClip response using a binary partition for MR (≤ mild [1+]), rather than a single quantitative measure. This approach is consistent with that employed in several prior studies in which greater severity of MR after MitraClip was shown to confer adverse prognosis.3, 4 Despite this, a variety of cutoffs for adequate MR reduction have been used in prior MitraClip studies, which may explain variable rates of recurrent MR.2-4, 20-23 Of note, procedural success among our cohort (41%) was near equivalent to that among degenerative MR patients undergoing MitraClip in the the EVEREST II trial, in which 43% of patients had ≤ mild MR at 1 year followup.2 ” (page 16, lines 6-13)

Of course, if there are any other specific additions to the manuscript that the reviewer feels warranted, we would be happy to add these.

2. Please provide the years taken into consideration for patient’s selection. How many patients were treated with MitraClip overall in those years? What were the most common reasons for exclusion? Please provide a flow chart.
We appreciate this insightful comment. Our study encompassed consecutive patients undergoing MitraClip who had pre- and post-procedural transthoracic echo, so as to test device-effects on mitral annular geometry (as well as adverse remodeling as a predictor of MR recurrence) among a broad population reflective of general clinical practice: No patients were excluded based on imaging, procedural, or clinical characteristics. Patients undergoing MitraClip between 2013 and 2019 were included in our study. While it is certainly true that clinical considerations and/or published trial results (e.g. EVEREST) could have influenced decisions to refer for MitraClip, we do not have access to objective data with which to categorize such factors. We have modified our text to better clarify inclusion criteria for our study, as well as % of patients undergoing MitraClip during the study interval who were included in study analyses: “The study population comprised consecutive patients with advanced (&gt;moderate) MR who underwent MitraClip at Weill Cornell Medicine (NY, NY) in whom intraprocedural TEE was available to evaluate annular geometry and TTE was performed pre- and post- (1-6 months [target 6 months]) procedure to assess change in MR: No otherwise eligible patients were excluded based on procedural outcomes, imaging findings, or clinical indices” (page 6, lines 2-6).

Given that our study aimed to examine MR response to MitraClip, patients who did not have follow-up echo follow-up at our center (to assess change in MR) were not included in this study. Our revised manuscript now reports the population as a % of all patients who underwent MitraClip during the study interval:

“The study population comprised 80 patients with advanced (&gt;moderate) MR who underwent MitraClip as well as pre- and post-procedure TTE to assess procedural durability, reflecting 78% of all patients who underwent MitraClip implantation at our site during the study interval (2013-19)” (page 9, lines 3-6).

3. Was the impact of MitraClip on annular geometry consistent across the different etiologies for MR? I would expect for example a different impact in calcified annuli when compared to subjects with mitral valve prolapse.

We fully appreciate the importance of this issue and have performed additional analyses to address this.

Table 6 in the revised manuscript has been substantially expanded, and now provides subgroup analyses among patient groups with mitral valve prolapse and prominent annular calcification. Our analyses demonstrate that MitraClip acutely produced changes in annular geometry in each sub-group, as evidenced by decreased annular area, circumference, and linear dimensions (all p&lt;0.001). Of interest, device-induced effects on tenting geometry did differ between patients with and without prolapse, as evidenced by significant reductions for these indices in the overall population (p&lt;0.05), but non-significant differences in pre- and post-procedural tenting indices among patients with prolapse. The revised manuscript has been expanded to include text, which summarized these findings:

“Of note, Table 6 also demonstrates that MitraClip induced changes in annular geometry (area, circumferential, and linear indices) generally were similar among patient subgroups with mitral prolapse (n=19) and prominent annular calcification (n=25) – although device-induced
reductions in tenting indices were non-significant in patients with prolapse” (page 11, lines 19-22).

We again thank the Reviewer for this extremely helpful and insightful suggestion.