Author’s response to reviews

Title: Pericardial Closure with Extracellular Matrix Scaffold Following Cardiac Surgery Associated with a Reduction of Postoperative Complications and 30-day Hospital Readmissions

Authors:

Alfredo Rego (Alfredo.Rego2018@gmail.com)

Patricia Cheung (pccheun@emory.edu)

William Harris (wjharris3@me.com)

Kevin Brady (bradycardiac@gmail.com)

Jeffrey Newman (jhnewmanmd@yahoo.com)

Robert Still (rjstill3@comcast.net)

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Author’s response to reviews:

Reviewer #1: The authors performed an observational multicenter cohort study to evaluate the clinical outcomes of pericardial closure using a decellularized matrix patch comparing patients in the study cohort with a patient cohort from a national database using inverse probability weighting for adjustment of baseline covariates.

The study area is relevant as no consensus exist to whether or not the pericardium should be closed. Furthermore, different techniques for pericardial closure have been described both in animal studies as well as in clinical studies.

I have some comments and suggestions regarding the manuscript:

Title: The title of the paper "Pericardial Closure with Extracellular Matrix Scaffold Following Cardiac Surgery Reduces Postoperative Complications and 30-day Hospital Readmissions" indicates a cause-relationship between the use of the pericardial patch and a reduced proportion of patients with pleural and pericardial effusion and 30-day readmission. However, this study was an observational study, and this study design can only point towards "associations". The title should therefore be: "Pericardial Closure with Extracellular Matrix Scaffold Following Cardiac Surgery is Associated with a Reduction of Postoperative Complications and 30-day Hospital Readmissions".
Re: The title was revised as suggested to “Pericardial Closure with Extracellular Matrix Scaffold Following Cardiac Surgery Associated with a Reduction of Postoperative Complications and 30-day Hospital Readmissions”.

Abstract: The authors provides the readers with an informative and balanced summary of what was done and what was found, but the conclusion should be changed in accordance with the comments given above regarding the title stating an association instead of indication a cause-effect between pericardial closure with ECM and complications.

p-values are given for some significant results but not for all significant results mentioned in the abstract. P-values could be mentioned for all the results.

Re: The results section of the abstract was revised to include p-values for all significant results. Also, the conclusion was changed as suggested to state that pericardial closure with ECM following cardiac surgery is associated with a reduction in the proportion of patients with pleural effusion, pericardial effusion and 30-day readmission.

Results: A total of 1,420 patients at 42 centers were enrolled, including 923 coronary artery bypass grafting (CABG) surgeries and 436 valve surgeries. Significantly fewer valve surgery patients in the RECON cohort experienced pleural effusion (3.1% vs. 13.0% p<0.05) and pericardial effusion (1.5% vs. 2.6%, p<0.05) than in the NRD cohort. CABG patients in the RECON cohort were less likely to suffer bleeding (1.2% vs. 2.9% p<0.05) and pericardial effusion (0.2% vs. 2.2% p<0.05) than those in the NRD cohort. The 30-day all-cause hospital readmission rate was significantly lower among RECON patients than NRD patients following both valve surgery (HR: 0.34; p<0.05) and CABG surgery (HR: 0.42; p<0.05). In the RECON study, 14.4% of CABG patients and 27.0% of valve patients had postoperative atrial fibrillation as compared to previously reported risks, which generally ranges from 20% to 30% after CABG and from 35% to 50% after valve surgery.

Introduction: A sufficient background and rationale for the investigation is reported and a specific objective of the study is stated. A prespecified hypothesis is missing.

Re: A hypothesis was added to the end of the Introduction section as detailed below.

It is hypothesized that closure of the pericardium with ECM will reduce readmission rates and perioperative complications in patients undergoing CABG or valve repair and replacement when compared to a nationwide readmission database.

Methods: The study design is sufficiently described, but important definitions regarding clinical outcomes in the RECON group are missing. In the "Limitations section" the authors importantly acknowledge that definitions of outcomes may differ between the study groups.
How were pleural and pericardial effusions defined? Was only effusions needing treatment registered or were all effusion diagnosed by CT scans, x-ray of the chest or diagnosed by the use of ultrasonography registered?

Re: The Methods section of the manuscript was revised as detailed below to add definitions for pleural and pericardial effusions in the RECON group. Pleural effusion was noted on the case report forms for those patients that required a thoracentesis or had imaging performed to confirm pleural effusion. Pericardial effusion was noted for those patients that experienced clinical tamponade or required pericardiocentesis.

How were new-onset postoperative atrial fibrillation diagnosed (single ECGs? continuous monitoring? Holter?) and defined (POAF of any length?). Were only POAF needing treatment registered?

Re: The Methods section of the manuscript was revised to add a definition for postoperative atrial fibrillation. In RECON, postoperative atrial fibrillation included all patients that had any notation of postoperative atrial fibrillation in their medical record from the time of surgery through the date of follow-up. All patients were on continuous monitoring until hospital discharge. POAF was also noted in the patient record if complications occurred and an ECG confirmed atrial fibrillation.

POAF was noted on the case report form for those patients that had any notation of AF in the medical record from the time of surgery through the date of study follow-up.

How was postoperative bleeding measured? Total drainage amount? or number of patients re-operated due to bleeding?

Re: The Methods section of the manuscript was revised as detailed below to add a definition for bleeding in the RECON group.

Bleeding broadly included all patients experiencing any bleeding complication that required intervention, such as return to the operating room.

Line 112: outcome measures included 30-day readmission ….. should be … 30-day all-cause unplanned readmission..(In the result and discussion section it is mentioned that readmission means all-cause readmission)

Re: The Methods section was revised to state 30-day all-cause unplanned readmission as recommended.

Basic information regarding routine surgical techniques are missing. Were all CABG procedures performed on-pump? Was any pharmacological methods used as a routine in order to reduce postoperative bleeding and were other efforts used in general in order to reduce postoperative bleeding? Do the authors have any general information about this? This information is important in relation to the external validity of the study - even if the study was a multicenter study.
How were chest tubes used? Did the centers routinely place chest tubes in the pleura space if opened? As early chest tube removal is associated with pleural and/or pericardial effusion it would also be interesting to have information on when chest tubes were removed as a routine. Do the authors have any information about this? There were probably also some differences between hospitals.

Re: Limited information is available regarding routine surgical techniques used for patients in the RECON group. Nearly all patients enrolled had a chest tube placed internal to the pericardium during the procedure. Time to chest tube removal was not captured. Since this data was not available for those patients in the NRD, it was not included in the manuscript.

Clear information are provided regarding data for the control group retrieved from the National Readmission database Cohort.

Statistical methods: The authors should explain how the study size was arrived at.

Re: The study was designed to be a post-market observational study aimed to collect important clinical outcome information and compare these outcomes with the “real world” data. Since this was not a randomized clinical trial, a power analysis was not performed to determine the sample size.

The authors used inverse probability of treatment weights to account for any potential imbalance of baseline demographic and comorbidities. I will leave the evaluation regarding how this specific type of propensity score technique was used to a statistical reviewer, but the idea using a propensity score model for balancing the distribution of measured potentially confounding covariates is appreciated.

Results: A total of 1,420 patients were enrolled in the RECON study. Why were only results from patients undergoing isolated CABG and valve patients ± CABG reported in the present study?

Re: Most Patients (1,359 or 95.7%) enrolled in the study underwent CABG and/or valve procedures. Only 61 enrolled patients underwent procedures that did not include CABG or valve repair/replacement and a variety of different procedures were performed for these patients. The more common procedures included mass removal, LVAD implantation, and atrial septal defect repair. The small number of patients enrolled in each of these groups did not warrant an individual analysis for each procedure type.

Do the authors have any information regarding the main reasons for re-admissions?

Re: The leading causes for readmission in the RECON cohort are pleural effusion, pericardial effusion, CHF, arrhythmia including POAF, and sternal dehiscence or infections. In the NRD 2014 cohort, pleural effusion was found in 22% of CABG readmissions and 25% of valve readmissions. The #1 procedures that were performed in CABG and valve readmissions were thoracentesis. However, in the NRD registry, each readmission event was associated with
multiple diagnosis codes without clear indication of the reason for readmission. The design of the NRD register also includes the presence of comorbidities and risk factors in the readmission diagnosis. Therefore, the comparison of reasons for readmission between two groups cannot be conducted.

In line 230 it is stated that pericardial closure using ECM also reduced 30-day all-cause unplanned readmission. The implies a course-effect relationship, but only associations can be identified in observational studies. I suggest that the text is modified to …pericardial closure is also associated with …

Re: The statement was revised per the recommendation to state that pericardial closure with ECM was also associated with reduced 30-day all-cause unplanned readmission following valve procedures.

Discussion: In the first section it is mentioned that 1,420 patients were enrolled and the readers will get the impression that all patients were included in the analyses which they were not. The authors should also mention the number of patients that were actually included in the analyses of the reported study.

Re: The statement in the Discussion section was revised as suggested to include the number of patients in the RECON CABG and valve repair/replacement groups.

The clinical outcome for 866 CABG and 392 valve repair/replacement patients in RECON was compared to the NRD with 57,364 CABG patients and 42,269 valve repair/replacement patients.

Line 248-249: In this sentence indicates a cause-effect. The sentence should be modified to …. pericardial closure is associated with a significant reduction in the 30-day all-cause unplanned readmission rates. In lines 258-260 the authors are discussion a potential background for a cause-effect, which is appreciated.

Line 296-297: the text should be changed to indicate an association and not a cause-effect between closing the pericardium and a reduced incidence of pleural effusion

Re: The statements were revised as suggested to state that pericardial closure with ECM was also associated with reduced 30-day all-cause unplanned readmission following isolated CABG procedures.

Important limitations of the study are acknowledged by the authors.

A short discussion of generalizability of the study results outside USA would be nice. Databases may be more related to use of resources in USA compared to database information in e.g. Scandinavia.

Re: A discussion of the limitations of the study results outside the US was added to the Limitations section and is included below.
It is also important to reiterate that the data in the present study include outcomes only from patients treated the United States only. Although pericardial closure following cardiac surgery is not standard of care in the United States, this surgical practice is more common in other countries. As a result, complication rates presented in the NRD may differ from those rates of other countries and further study may be necessary to confirm these findings using a European patient cohort.

Conclusion: The conclusion should be changed indicating an "association" between pericardial closure and the outcomes of interest, as an observational study does not provide data in order support a conclusion indication that pericardial closure was the cause of a reduced proportion of patients with complications.

Re: The statement in the Discussion section was revised as suggested.

In conclusion, this study demonstrated that pericardial closure using ECM following cardiac surgery is associated with a reduction in 30-day all-cause readmission and postoperative complications including pericardial effusion, pleural effusion and bleeding without any observed negative impact on patient safety.

References: References referred to in the text should be given in a single paragraph, and the reference style doesn't seem to comply with the guidelines for authors.

Re: The references in the manuscript have been updated to the Vancouver reference style per journal guidelines.

Reviewer #2: I congratulate the authors for this interesting article. Overall it is nicely done study. Certainly, it contributes to the field.

Only very few comments to be in the authors considerations:

1. Please clarify the inclusion and exclusion criteria for the studied patients.

Re: The study was designed to collect data at the enrolling sites for all patients at that had their pericardium closed using ECM after cardiac surgery. Only those patients that did not consent to data collection were excluded from enrollment. Additional information was added to the Methods section to provide clarification.

In the RECON study cohort, all patients with pericardial closure using ECM after cardiac surgery willing to provide informed consent were eligible for enrollment in the study. There were no other inclusion or exclusion criteria defined for the study.
2. Page 6 line 82- 85 ProxiCor™ (Aziyo Biologics, Inc.) is a bioresorbable, de....) Not referenced.

Re: A reference was added to support the statements about ProxiCor ECM.

3. did the authors re-operated upon any patients later during the study period and noticed any change regarding the extent of adhesions compared with the patient with non closed pericardium. Is there any plan to study this issue?

Re: Unfortunately, no re-operation data was collected for the study. We are not aware of any ongoing or planned studies evaluating adhesions in patients that have had pericardial closure using ECM.

Reviewer #3: The authors report the experience after introducing an extracellular matrix patch for pericardial closure in a multi-center study. The study contains 42 centers and the study population was compared to a national database. The Authors have clearly expended a lot of time and effort to collect all the data, which the authors lead to quite remarkable conclusions. Although I do not agree with all of those conclusions, some of them need to be proven better, the authors show a significant reduction of readmissions and pericardial or pleural effusions.

1. Abstract: The abbreviation „POAF” (post-OP atrial fibrillation?) should be explained. In general, I would suggest reducing all figures to the absolute minimum in the abstract section.

Re: The abbreviation “POAF” was changed to “postoperative atrial fibrillation” in the abstract.

2. Line 77 - 79: Be careful with your statement that pericardial closure is only performed in a small portion of cardiac surgeries. That may be the case in the States, but this is a worldwide read journal and in other parts of the world it is the standard of care to close the pericardium. I would suggest rephrasing that part.

Re: Thank you for pointing this out. The background section was revised to clarify that pericardial closure following cardiac surgery is performed in only a small portion of the surgeries in the United States. A statement was also added to the Limitations section for further clarification.

Although available clinical evidence demonstrates that pericardial closure following cardiac surgery is safe and improves patient outcomes, in the United States, it is only performed in a small portion of cardiac surgeries.

3. I would suggest focusing on one or two groups of patients, not mixing the aortic valve replacement patients with the repair patients (see my remark no. 9). Repair and replacement patients are very much different patients and to mix the results is questionable.
Re: The purpose of this study is to understand the effect of pericardial closure in cardiac surgery, where isolated CABG and valve replacement/repair represent two major sub-groups of patients with different risk levels and procedures. We agree with the reviewer that the valve replacement/repair cohort represents a population of patients with different risk levels and operation techniques/implants. In addition, the isolated CABG cohort also represents different subgroups defined by number of bypassed blood vessels and different technique used. Further stratification would definitely be beneficial to understand the impact of pericardial closure in each group. However, the readmission and complications studied here are relatively rare events which requires large samples sizes to have enough statistical power. Thus, further stratification of the 392 valve patients into the sub groups (for example, 168 aortic valve replacements) is not feasible for this analysis. We agree with the reviewer that this could be a potential limitation in this study, and the following was added to the Discussion:

“Furthermore, the limited sample size in the RECON valve repair/replacement cohort prevented further patient stratification into valve repair and replacement sub-groups. Valve replacement and repair have different operation techniques and risk levels, thus the effect of pericardial closure might be different in these two group. Further study is necessary to study the outcome of pericardial closure in these sub-groups.”

4. Line 108 - 111: Please comment on the method how you gained the information about pleural or pericardial effusion and atrial fibrillation when you see the patients after 30 days for the first time since discharge.

Re: Patients were enrolled in the study at their follow up visit after discharge and consent was granted by patients allowing clinical site personnel to provide all applicable information from their medical record. Definitions for atrial fibrillation and pleural and pericardial effusions were added to the Methods section to clarify. Any pleural effusions requiring imaging or thoracentesis and pericardial effusions requiring pericardiocentesis or notes of clinical tamponade were included. Patients underwent continuous monitoring.

5. Line 115 - 117: In my opinion, there should have been a study protocol defining exactly what a device-related event is. I am not sure if all surgeons in the 42 participating centers deem the same events as device-related.

Re: Although it is certainly possible that investigators may have differing views on the relatedness of an event, there was a definition included in the study protocol detailing the definition for device-related events. Additional details were added to the Methods section of the manuscript as detailed below.

Safety outcomes were determined by analysis of all device-related adverse events. Device-related events were defined as clinical signs, symptoms or conditions that were deemed by the investigator as causally related to the device implantation procedure, or the presence or performance of the ECM device. Events were considered device-related if, due to the temporal proximity of the adverse event to ECM device implantation, there was a reasonable possibility
that the device may have caused the event or may have contributed to the severity or duration of an event caused by other means.

6. Line 186 - 191: You have referred to the table. No need to repeat all the information.

Re: Removed the procedure information from the Results section that was duplicated in Table 1.

7. Line 215: Why have been the 17 patients readmitted? Is there any possibility to get the equivalent data from the registry? I think when stating a lower readmission rate we must know why the patients have been readmitted.

Re: The leading causes for readmission in the RECON cohort are pleural effusion, pericardial effusion, CHF, arrhythmia including POAF, and sternal dehiscence or infections. In the NRD 2014 cohort, pleural effusion was found in 22% of CABG readmissions and 25% of valve readmissions. The #1 procedures that were performed in CABG and valve readmissions were thoracentesis. However, in the NRD 2014 registry, each readmission event was associated with multiple diagnosis codes without clear indication of the reason for readmission. The design of the NRD register also includes the presence of comorbidities and risk factors in the readmission diagnosis. Thus, the comparison of reasons for readmission between two groups cannot be conducted.

8. Line 258 - 260: See above: as long as you do not know why the patients have been readmitted, there could be hundreds of reasons for the lowered incidence of readmissions. Furthermore, when speaking about a lower incidence of pericardial effusion, you should keep in mind, that different operation techniques and implants produce different amounts of fluids, e.g. when performing an aortic valve repair often the used aortic prosthesis produces pericardial effusion. For that reason, I might be tempted to suggest that you either distinguish between aortic valve repair and replacement or concentrate on one group.

Re: As discussed earlier, the leading causes for readmission in the RECON cohort are pleural effusion, pericardial effusion, CHF, arrhythmia including POAF, and sternal dehiscence or infections. We agree with the reviewer’s comments that this study cannot establish a definitive cause-effect relationship between pericardial closure and reduction in admission. We have changed our conclusion to “this study demonstrated that pericardial closure using ECM following cardiac surgery is associated with a reduction in 30-day all-cause readmission” throughout the manuscript.

As discussed in Reviewer’s comment #3, the limited samples size prevented us from performing further stratification and the limitation was added to the manuscript.

9. Line 273 - 277: I would be very careful with those conclusions as they do not include the blood coming from the intrapericardial sutures. A barrier for the blood works in two ways,
preventing blood to drain from the pericardium into pleura and thus prolonging the blood-atrium contact.

Re: Thank you for your comment. The statements at lines 273-277 are intended to provide a discussion around one possible mechanism of action for the reduction in POAF observed in patients that had their pericardium closed using ECM. In the RECON studies, 95% of the patients enrolled had a chest tube placed internal to the pericardium during the procedure to allow blood drainage from the pericardium. The tube placement information was added to the manuscript.

10. In general: When you write about pericardial or pleural effusion, are you talking about ml drainage, readmission for effusions, reoperation for effusions or TEE/TTE findings? Please clarify.

Re: The Methods section of the manuscript was revised to add definition for pleural and pericardial effusions. In RECON, pleural effusion was noted on the case report forms for those patients that required a thoracentesis or had imaging performed to confirm pleural effusion. Pericardial effusion was noted for those patients that experienced clinical tamponade or required pericardiocentesis.