Peer Review File

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Reviewer A

Comment 1: In my opinion the article is well constructed, and the objective emerge clearly: to demonstrate the superiority of the new vein storage solution versus normal saline solution.
Reply 1: Thank you for your kind comment.

Comment 2: Firstly, I think that the study design doesn't appear as the appropriate one, it seems difficult to control biases using two different patient populations: a retrospective cohort as per control group and a prospective cohort as per treatment group. In this scenario, the correct procedural steps should have been to define the patient population and all co-variates to include in the PS system to control biases before starting the patient's enrollment in the prospective study; therefore, two arms should set forward simultaneously, the treatment group and the control group.
With the method adopted by authors the PS analysis include few variables to could conclude that the two group are comparable, as the same authors explain in the limitations paragraph.
Reply 2: I respectfully disagree with the previous comment, as the statistical justification raised by the reviewer seems to be incorrect. While I acknowledge that a prospective clinical trial would have been the most appropriate method for this study, it is important to note that such a methodology can be both expensive and challenging to implement. In a prospective clinical trial, as the reviewer suggested, propensity score matching is not necessary or recommended, as the randomization process ensures that different confounders are equally distributed among the study groups. Propensity score matching is a process used to establish comparable study groups that have been retrospectively included. This matching method is widely accepted and utilized in scientific publications, with thousands of studies employing this validated approach. In the context of a retrospective cohort study, propensity score matching attempts to compensate for the absence of randomization by creating comparable cohorts with respect to known potential confounders.
Changes in the text: None.

Comment 3: Secondly, 90 patients only per group it appears a too small size sample to reach statistical significance level to demonstrate the superiority of one solution taking into account the above-mentioned study design errors.
Reply 3: I acknowledge that one of the main limitations of our study is the relatively small sample size, which may have implications for the statistical power to detect clinical differences. The study was designed with a sample size of 90 patients in each group, resulting in a power of 54% (based on a 1:1 ratio, observed event rates of 10% and 21.1% for the primary endpoint). It is important to note that with a small sample size, there is a possibility of incorrectly concluding no impact of the treatment arm, as we would have a 46% probability of committing a type II error. However, despite the limitations of the sample size and statistical power, we were able to identify significant differences. This suggests that the observed statistical significance, despite the low power and small sample size, may indeed reflect a clinically effective impact of the treatment arm.
Changes in the text: The low power of the study was explicitly mentioned in the manuscript's limitations section (Page 14, line 295).

Comment 4: Moreover, more issues should be addressed: the high rate of OPCAB procedures and endoscopic vein harvesting in a relatively small CABG center (400 procedures in a period of 5 years) could involve technical challenges that weight-on results, especially because authors don't have investigated graft patency but only clinical outcomes.

Reply 4: At our institution, it is our standard practice to routinely perform CABG using the OPCAB technique, and the majority of vein grafts are harvested using the endoscopic approach. The OPCAB procedures are primarily conducted by two highly experienced surgeons who possess extensive expertise in OPCAB surgery. It is noteworthy that over 90% of our CABG procedures are performed without the use of cardiopulmonary bypass (CPB), with less than 1% reconversions to on pump surgery. It is important to acknowledge that the debate regarding on-pump versus off-pump CABG is ongoing and falls beyond the scope of our current manuscript. The existing medical literature suggests that both procedures are comparable when performed by experienced hands. Furthermore, the use of endoscopic vein harvesting is recommended in experienced centers, as supported by the 2018 EACTS guidelines, and has demonstrated comparable graft patency to open surgical harvest (N Engl J Med 2019; 380:132-141).
Besides, as reported in the text, the use of OPCAB or endoscopic vein harvest did not affect event free survival: "three-year freedom from MACE was similar between patients who underwent surgery on-pump and off-pump (IRR 0.61; 95% CI 0.24-1.84, p=0.29). We also found that EVH did not affect three-year freedom from MACE (IRR 0.80; 95% CI 0.2-2.3, p=0.73)".

Changes in the text: None

Comment 5: …especially because authors don't have investigated graft patency but only clinical outcomes. It doesn't clearly emerge the direct correlation with the use of a storage vein solution and clinical outcomes if the outcome, itself, is not confirmed to be dependent on vein graft patency.
Reply 5: I completely agree that vein patency was not assessed, and it is reflected in the limitations section.
Changes in the text: None.

Comment 6: In conclusion, the idea to investigate the effect on long-term outcomes and patency of this endothelial damage inhibitor solution is good, the way to do it should be different and in this form I don't think the article reaches the target of publication.
Reply 6: In conclusion, while I appreciate the reviewer's perspective, I respectfully disagree with their comment regarding the suitability of the manuscript for publication. The primary aim of our study was to investigate the effect of the endothelial damage inhibitor solution on long-term outcomes and graft patency. Although the reviewer raises valid concerns about the study design and sample size, I believe that the limitations and challenges were adequately addressed in the manuscript. Ultimately, it is the prerogative of the editor-in-chief to determine the suitability of the manuscript for publication, considering the overall scientific merit and contribution of the study to the field.
Changes in the text: None

Reviewer B

Comment 1: The manuscript is intriguing, methodologically sound and timely. Authors well described strengths and weaknesses of the paper and its role as hypothesis generating. All in all, it might deserve publication in the present form.
Reply 1: Thank you for your positive and encouraging comment. We sincerely appreciate your recognition of the manuscript. We have made every effort to thoroughly present the strengths and weaknesses of our study and acknowledge its role as a hypothesis-generating work. Your suggestion that the manuscript deserves publication in its current form is truly appreciated.

Reviewer C

Comment 1: In my opinion the article is well constructed, and the objective emerge clearly: to demonstrate the superiority of the new vein storage solution versus normal saline solution.
Reply 1: Thank you for your kind comment.

Comment 2: “The 13 patients that were off support in the EDI group” – what do you mean by “off support”? that’s unclear.
Reply 2: I apologize for the confusion caused by the term "off support." In this context, "off support" refers to those patients in the EDI group whose calculated propensity score could not be matched with a control patient who had an equivalent score. These patients in the EDI group had a calculated score that fell outside the defined maximum caliper distance, which was set at 3% standard deviation. Consequently, these patients were not included in the study sample, as their baseline characteristics would differ from those of the control group.
Changes in the text: The term off support was eliminated, and a clearer definition of the excluded patients was added (Page 7 line 115).

Comment 3: I’d like to see the calculated power of the study in the methods section. 90 patients in each group seems like a small number to have adequate power to prove your hypothesis. You also did subgroup analysis with even smaller groups – I’m not sure that could be justified even if they were prespecified.
Reply 3: Thank you for your comment and raising the concern about the calculated power of our study with a sample size of 90 patients in each group. We appreciate your attention to detail. I would like to clarify that the subgroup analysis performed in our study was indeed prespecified as part of our research plan. These subgroup analyses were included to explore potential effects within specific patient subsets and provide valuable insights.
While it is true that the sample sizes in some of the subgroups were smaller, they were still within the predefined criteria for analysis. However, we acknowledge the inherent limitations associated with smaller subgroup sizes and the need for cautious interpretation of the results.
Changes in the text: Added clarification regarding the prespecification of the subgroup analyses and addressing the concern about smaller sample sizes (Page 14, Line 295).

Comment 4: In the limitations you state “Another limitation is the fact that vein patency was not assessed in every patient, therefore, the observed MACE cannot be directly related to vein graft occlusions.” – was patency assessed in some patients? If so, where is the data in the manuscript? It’s invaluable to your discussion.
Reply 4: I am sorry to inform that vein patency was not assed in all the observed events. The only data we have is that out of the 5 patients that required revascularization, 3 of them had an occluded vein grafts (2 in the conventional treatment arm). Nevertheless, this are very low numbers to draw any conclusion.
Changes in the text: This comment has been added to the limitations section (Page 15, Line 335).

Comment 5: Do you use TTFM for intraoperative graft assessment? If so, you should describe that in the methods section.
Reply 5: Thank you for bringing up this important point. We appreciate your suggestion regarding the inclusion of TTFM (Transit-Time Flow Measurement) for intraoperative graft assessment in the methods section. We would like to clarify that TTFM is indeed routinely used in our institution to assess graft flow and pulsatility in every CABG procedure. We acknowledge the importance of describing this technique in the methods section to provide a comprehensive understanding of our methodology. In response to your comment, we have made the necessary addition to the methods section to explicitly mention the routine use of TTFM for intraoperative graft assessment.
Changes in the text: We have included a statement in the methods section to highlight the routine use of TTFM for intraoperative graft assessment (Page 8, Line 150).
Comment 6: You discuss briefly in your paper the effect postoperative medications have on vein graft patency. Please add to the paper your protocol (aspirin only? DAPT with clopidogrel?) and, if the data is available, the post op medications patients were given according to group.
Reply 6: Thank you for your comment regarding the discussion of postoperative medications and their effect on vein graft patency in our paper. We appreciate your interest in our protocol and the medications given to patients in each study group.

In our institution, every CABG patient is discharged home with Dual Antiplatelet Therapy (DAPT) for a duration of 12 months, along with high-dose statins. The DAPT regimen consists of aspirin in combination with clopidogrel. It is important to note that both study groups adhered to this institutional protocol, with a 100% completion rate.
We have incorporated this information into the methods section to provide clarity on our postoperative medication protocol and its uniform implementation across both study groups.
Changes in the text: We have included this information in the methods section to describe the postoperative medication protocol, including DAPT with aspirin and clopidogrel for 3 months, along with high-dose statins. Additionally, we mentioned the 100% completion rate of this institutional protocol in both study groups (Page 8, line 155).

Comment 7: According to table 3 the main difference between the groups occurred in the first year because of recurrent angina and repeat revascularization. Can you explain how this difference is explained by the use of an EDI that is supposed to prevent long term intimal hyperplasia and inflammation. Short term vein graft failure is usually related more to technical errors than to intimal hyperplasia.
Reply 7: We appreciate your observation regarding the main difference between the study groups observed in the first year, specifically related to recurrent angina and repeat revascularization as shown in Table 3. We agree that short-term vein graft dysfunction is often attributed to technical errors rather than intimal hyperplasia.
It is important to note that the use of an endothelial damage inhibitor (EDI), such as DuraGraft®, aims to prevent long-term intimal hyperplasia and inflammation, which are associated with graft failure in the later stages. However, in the short term, graft dysfunction can be influenced by factors related to graft preservation and endothelial integrity.
Preservation of vein grafts in normal saline can lead to graft injury, impairing physiologic function and viability. In contrast, the use of preservation solutions, such as DuraGraft®, has been shown to mitigate graft dysfunction by reducing nitro-oxidative stress and the expression of ICAM-1, without leukocyte engagement. These benefits contribute to maintaining endothelial integrity and function, thus potentially reducing short-term graft-related complications.
While the observed difference in recurrent angina and repeat revascularization in the first year may not be solely explained by intimal hyperplasia, the use of an EDI like DuraGraft® is aimed at preventing long-term complications associated with intimal hyperplasia and inflammation.
Changes in the text: A comment was added in the discussion regarding this point (page 14, line 255).

Comment 8: Tables – please add the total number of patients in each group at the top of each column.
Reply 1: The total number of patients was added at the top of each column.
Changes in the text: Tables were modified accordingly.

Comment 9: Table 3 – there is a typo in HTN.
Reply 9: The typo was corrected.
Changes in the text: The typo was corrected.

Reviewer D

Comment 1: It is well-Known that saline solution, an acid solution, is dangerous for venous endothelial cells and that other solutions, like buffered solutions, may be more effective. Nowadays, the aim is to find the best preservation solution to preserve the endothelial layer to prevent vein graft disease and, therefore, vein graft failure.
Reply 1: I wholeheartedly agree with your comment, and we appreciate your insight into the detrimental effects of saline solution on venous endothelial cells. Indeed, it is widely acknowledged that other solutions, such as buffered solutions, offer potential advantages in preserving the endothelial layer to prevent vein graft disease and, ultimately, vein graft failure.

We have already acknowledged this limitation in the manuscript's limitations section, emphasizing the ongoing pursuit to identify the optimal preservation solution.
Changes in the text: None.

Comment 2: Patients did not perform a coronary angiography imaging modality or a computed tomography coronary angiography to evaluate the vein graft patency. So, the actual incidence of the observed MACE cannot be directly related to vein graft occlusions.
Reply 2: I appreciate your comment and agree with the concern raised. It is true that we did not utilize coronary angiography or computed tomography coronary angiography to directly evaluate vein graft patency in our study. Therefore, the observed incidence of major adverse cardiac events (MACE) cannot be solely attributed to vein graft occlusions. This limitation has been explicitly acknowledged in the limitations section of our manuscript.
Changes in the text: None.

Reviewer E

Comment 1: I suggest that the authors include "Duragraft" in the abstract. It isn't clear what the authors mean by "endothelial damage inhibitor preservation solution".
Reply 1: The text was modified as suggested.
Changes in the text: The term Duragraft was added in the abstract (Page 3, Line 31).

Comment 2: Introduction: The first paragraph can be deleted - it is very generic.
Reply 2: Thank you for your suggestion regarding the first paragraph of the introduction. I agree that the paragraph is too generic and can be deleted to improve the focus and specificity of the introduction.
Changes in the text: The first paragraph of the introduction has been removed as per your suggestion.

Comment 3: The conventional method of graft preservation was used in 2014-5, Duragraft was used in 2016-8, and conventional was used in 2019. Given that the 2 methods of graft preservation were each used for 3 years, why was there such a difference in the numbers of patients who were treated with each method? I thought that Duragraft was used exclusively in 2016-8. If both solutions were used in 2016-8, please include the strategy to use one solution vs the other. Why was Duragraft not continued in 2019?
Reply 1: Thank you for bringing up this point regarding the difference in the numbers of patients treated with each graft preservation method and the discontinuation of Duragraft in 2019. Allow me to clarify the timeline and reasons behind these observations. Duragraft was used exclusively in every patient from December 14, 2016, until November 5, 2018. In contrast, the control group consisted of patients who underwent CABG from January 2014 until the end of the study inclusion period in April 2019. Consequently, the use of Duragraft was limited to a two-year period due to its late introduction in late 2016. This discrepancy in patient numbers can be attributed to the timing of Duragraft availability. During the period when Duragraft was available, it was used in every CABG patient as per our institutional protocol. However, we faced limitations in the availability of Duragraft beyond November 2018 due to budget constraints and its restricted use for investigational purposes.
Changes in the text: None. We will consider adding the clarification provided in the previous comment to the main text if deemed necessary by the reviewer.

Comment 2: The authors used a limited number of variables in the PS logistic model. The model is usually populated with more variables.
Reply 2: Thank you for your comment. We acknowledge that the number of variables used in the propensity score logistic model was limited compared to the typical practice. However, our intention was to create a more parsimonious model to avoid collinearity and interactions among the selected variables. We carefully selected the variables that were clinically relevant and had a plausible effect on vein graft durability.

Changes in the text: We added a comment in the limitations section (Page 14, line 308).

Comment 3: It is conventional (but not universally accepted) to use statistics for matched data for analysis. The authors have used statistics for independent cohorts.
Reply 3: Thank you for your comment. We acknowledge that there are different approaches to analyzing matched data, and using statistics for independent cohorts is one of them. In our study, we chose to use statistics for independent cohorts for several reasons, including the availability of statistical software and the nature of our study design. We believe that this approach still provides valuable insights and allows for meaningful comparisons between the treatment and control groups.
Changes in the text: The comment was added to the Methods section (Page 9, Line 194).

Comment 4: The authors reported IRR. Why have the authors not determined the HR? The authors should include the point estimate for the IRRs and not just the 95% CIs where reported.
Reply 4: Thank you for your comment. We chose to report the incidence rate ratios (IRRs) instead of hazard ratios (HRs) because we had access to the Pearson time data for each patient. This allowed us to directly calculate the incidence rates in both cohorts. We have included the point estimates of the IRRs, in addition to the 95% confidence intervals, where they were reported.
Changes in the text: The point estimates of IRR were added were reported (Page 11, Line 233).

Comment 5: The authors should report the crude results as well as the PS matched results.
Reply 5: Thank you for your comment. I understand your suggestion to report both the crude results and the propensity score (PS) matched results. However, due to the study design, it is not feasible to present the crude results. The PS matching was conducted at the outset of the study to select patients for the analysis. Subsequently, the clinical follow-up data were collected for both cohorts simultaneously and blinded for treatment group adjudication. Unfortunately, we do not have access to the complete data of the patients who were not included in the PS matching process.
Changes in the text: None.

Comment 6: Discussion, paragraph 2: The first 3 sentences can be deleted - they are generic to CABG and not specific to this specific study.
Reply 6: Discussion - The first 3 sentences of paragraph 2 have been deleted as the reviewer suggested.
Changes in the text: The sentences have been deleted (Page 11, Line 243).

Comment 7: I recommend that the authors include substantially more variables to table 1. It is important to see how much bias there is for other variables. I acknowledge that Euroscore is a composite score derived from a number of risk variables.
Reply 7: Thank you for your suggestion. The purpose of Table 1 is to present the percentage of bias after matching for the covariates used in the calculation of the propensity score. It provides information on the balance achieved between the study groups. To provide a more comprehensive understanding of the baseline characteristics, Table 2 displays the actual differences among the study groups in various clinical variables relevant to CABG studies, as recommended. If the reviewer believes it is necessary, I am open to modifying Table 1 accordingly. Additionally, I would like to clarify that Euroscore 2 is a composite score derived from a logistic regression model incorporating several clinical and surgical characteristics.
Changes in the text: None.

Comment 8: Table 2: ICU length of stay is not normally distributed - SD>> mean. Suggest use median and IQR.
Reply 8: Thank you for your valuable suggestion. We have revised Table 2, page 22, to include the median and interquartile range (IQR) for ICU length of stay, as you recommended. Additionally, we have changed the statistical method used to compare the non-normally

distributed variables to the non-parametric Wilcoxon rank-sum test, which is appropriate for assessing the equality of such variables. These changes have been implemented to ensure accurate and meaningful representation of the data.
Changes in the text: Table 2, page 22 has been modified to include median and interquartile range (IQR) for ICU length of stay as suggested. The statistical method was changes to the non-parametric Wilcoxon rank-sum test to test the equality of non-normally distributed variables.

Comment 9: Figure 2: Is this the histogram prior of following matching? The histogram does not show a good overlap of the PSs.
Reply 9: Reply 9: Thank you for your comment. Figure 2 indeed represents the histogram of propensity scores after matching. While there is generally adequate overlap of the propensity scores, we acknowledge that there are four patients in the conventional treatment arm with propensity scores above 0.7 who do not have a matched pair in the treatment arm. It's important to note that these patients were matched using a caliper of 3% standard deviation with patients in the treatment cohort. Any patients whose propensity scores fell outside the pre-specified caliper were excluded from the matching process. The PS calculation was performed using Stata's user-written command PSMATCH2, and the specific syntax used is as follows: "psmatch2 Cohort EdadInt DiabetesBi HabTabBi Euro2 NumInjertos NumInjSafena OPCAB, outcome (MACE) neighbor(1) ai(1) noreplace caliper(0.03)." We appreciate your feedback and have made no changes to the text in response to this comment.
Changes in the text: None.

Comment: MACE: Tables and KM curves: The freedom from MACE in the control group drops off very early in year 1 and the 1-year estimate is much lower (82%) than what we usually expect post CABG at 1 year. The cumulative incidence of MACE is usually around 10% at 1 year post CABG - in FAME 3 was <<10%.
Reply 10: Thank you for your comment. The observed drop-off in freedom from MACE in the control group during the first year and the 1-year estimate of 82% may seem lower compared to what is typically expected post-CABG at 1 year. However, it's important to consider the characteristics of the patient population in our study. In Spain, the proportion of CABG procedures per million inhabitants is one of the lowest in the OCDE region. As a result, our institution primarily receives older patients with multiple risk factors, including diabetes, and complex coronary anatomy. The FAME trial, on the other hand, included a different patient population based on its specific inclusion and exclusion criteria, making direct comparisons challenging. Our study represents a real-life, all-comers CABG population, which may differ in terms of patient characteristics compared to clinical trials like FAME. The external validity of the FAME trial may be limited in patients with complex three-vessel disease and diabetes, as ethical restrictions may prevent their inclusion. Our 1-year MACE estimates align with previously published studies in similar contexts, such as the SYNTAX trial (NEJM 2009), which reported a 1-year MACE rate of 12.4%. Furthermore, it's worth noting that our patient cohort is older (mean age 69) and includes a higher proportion of diabetics (47%) compared to the FAME trial. Additionally, our cohort exhibits a very high surgical risk based on Euroscore 2 (mean Euroscore 2 for isolated CABG of 3.5%), further contributing to potential differences in outcomes. We appreciate your feedback and have made no changes to the text in response to this comment.
Changes in the text: None.

Reviewer F

Comment 1: First, the two groups are not well balanced since very few preoperative covariates were included in the propensity score matching model. The authors have included in the PSM model the following: age, DM, smoking history, number of distal anastomosis, number of vein grafts and mode of surgery (Off-pump or On pump CABG). It is largely reported that other factors are associated with accelerated vein failure graft such as hypertension, dyslypidemia, peripheral disease, COPD. These has to be included in the model to have more balanced groups.

Reply 1: Thank you for your comment. We acknowledge that other factors such as hypertension, dyslipidemia, peripheral disease, and COPD have been associated with accelerated vein graft failure. However, it is important to note that our propensity score matching (PSM) model was designed to create balanced groups specifically in the variables that were included, namely age, DM, smoking history, number of distal anastomosis, number of vein grafts, and mode of surgery (Off-pump or On-pump CABG). The goal was to minimize the confounding effects of these variables on the outcome of interest, vein graft durability.
While it is true that additional variables could potentially contribute to a more comprehensive assessment of group balance, it is crucial to strike a balance between including relevant variables and avoiding issues of collinearity and instability in the PS calculation. The variables included in our PSM model were chosen based on their clinical relevance and potential impact on vein graft durability.
Furthermore, we would like to clarify that the distribution of the other variables you mentioned, including hypertension, dyslipidemia, and COPD, were assessed in Table 2. We found no baseline differences between the two groups for these variables. As for peripheral arterial disease, the data for this variable was not included in Table 2, but we can confirm that there were no baseline differences in this variable either.
We appreciate your input and the suggestion to include additional variables. However, given the study design and the considerations mentioned above, we believe that the variables included in the PSM model adequately address the potential confounding factors related to vein graft durability.
Changes in the text: Table 2, Page 22 has been modified by the addition of baseline peripheral arterial disease.

Comment 2: Second, the rate of dual anti platelet therapy and the duration during the follow-up was not reported. DUAL therapy for at-least 1 year was associated with reduced vein graft failure, especially in OP-CABG surgery (which accounts for 84% in the population study).
Reply 2: Thank you for your comment regarding the discussion of postoperative medications and their effect on vein graft patency in our paper. We appreciate your interest in our protocol and the medications given to patients in each study group.
In our institution, every CABG patient is discharged home with Dual Antiplatelet Therapy (DAPT) for a duration of 12 months, along with high-dose statins. The DAPT regimen consists of aspirin in combination with clopidogrel. It is important to note that both study groups adhered to this institutional protocol, with a 100% completion rate.
We have incorporated this information into the methods section to provide clarity on our postoperative medication protocol and its uniform implementation across both study groups.
Changes in the text: We have included this information in the methods section to describe the postoperative medication protocol, including DAPT with aspirin and clopidogrel for 3 months, along with high-dose statins. Additionally, we mentioned the 100% completion rate of this institutional protocol in both study groups (Page 8, line 155).

Comment 3: Third, there is no hystoligcal analyses of vein graft between the two groups. Therefore the the results reported by the authors do not help to achieve strong conclusion. The association between the use of duragraft and better midterm results maybe due to casualty as we have no histological information about the cellular endothelium preservation with the use of duragraft solution.
Reply 3: Thank you for your comment. We acknowledge that histological analysis of vein grafts would provide valuable information regarding the cellular endothelial preservation between the two groups. However, it is important to note that this study was designed as a clinical observational study, and no additional tests or procedures beyond routine clinical practice were performed. Therefore, we did not have histological confirmation of endothelial preservation with the use of Duragraft or any other solution.
While histological analysis would have provided additional insights into the cellular endothelium preservation, the primary objective of our study was to examine the clinical outcomes and durability of vein grafts in patients treated with different preservation solutions.

We observed differences in the midterm results between the groups, which suggest a potential association between the use of Duragraft and improved outcomes. However, we acknowledge that these findings do not establish a causal relationship.
It is worth noting that previous experimental trials have reported on the histological confirmation of endothelial preservation with the use of Duragraft (DOI: 10.1080/17434440.2019.1682996). Our study aims to generate hypotheses and provide clinical observations based on real-world data. While histological confirmation would have strengthened our conclusions, it was beyond the scope and resources of this particular study.
Changes in the text: None.