논문의 정글에서 살아남는 법: Rebuttal Letter 작성법

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Disclosure

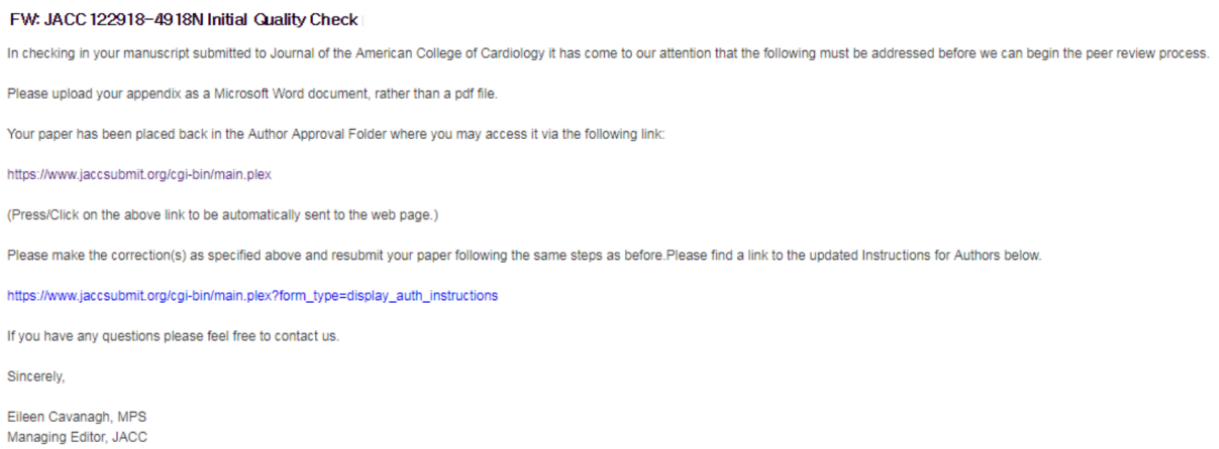
Relationships with commercial interests:

- Grants/Research Support/Lectures:
  - Abbott Vascular, Boston Scientific, Terumo, Philips Volcano, Medis Medical Imaging

- Consulting Fees:
  - Covanos, Emory University

Process of Peer Review System

- Manuscript submission by authors
- Initial quality check by editorial office staff (Instruction to authors)



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- Discuss – Keeper
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What is the criteria of the decision?

① Clinical relevance / Novelty
② Data and presentation quality
③ Make an issue in academic field
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⑤ Response to the Reviewers / Reviewer's opinion

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Criteria 1-4 : 이미 연구 시작단계에서 결정된다.

따라서 논문의 acceptance rate를 올리려면

Revision시 Reviewer 들에게 좋은 인상을 주어야 한다

Essential Factors in Rebuttal Letter

- Reviewer 들의 의도를 파악한다.
- 기본적으로 모든 요구는 100% 충족해주려고 노력해야 한다.
- 내가 가진 자료로 대응할 수 있는 것과 없는 것을 구분한다.
- 내가 가진 자료로 대응할 수 없다면, 시간/노력을 들여서라도 반드시 충족해야 하는 것과 Limitation에 기술하고 끝낼 것을 구분한다.
- Main results / Supplementary Results / Reviewer-Only Results를 구분한다.
- 어차피 나는 갑/을/병/정 중 "정" 이니 최대한 공손하게 문구를 작성한다.
- Revision과정에서 보완/추가한 원고는 Rebuttal letter에도 어느 곳에 어떻게 추가했다는 mention을 하여 최대한 성의 있게 보여야 한다.
- 아무리 harsh한 사람도, 인간인 이상 리비젼을 해서 보내면 처음보다는 덜 harsh해지기 마련…

Most Important Thing in Revision

논문의 Integrity (내가 가졌던 논문의 Core message)가 흔들려서는 안 된다.

리뷰어의 요구를 들어주다가 논문의 Integrity가 깨지면,
설령 publish되더라도, 나에게 의미 없는 논문이 된다.

Real Example: Response to General Comment

[General Comment] – 매우 호의적인 General Comment의 경우

This paper is a well done comprehensive work, which extends the observation of prior comparisons, now coupling them for the first time with clinical outcomes in a significant way. In addition, myocardial blood flow is measured by PET as opposed to other findings. The comparison to BSR and HSR are worthy, but omit the comparison to FFR for reasons which are unclear.

Response:

We thank you for all your valuable and positive comments. According to the Reviewer's comments, we tried our best to address each of the issues. We hope that these revisions fulfill the Reviewer's comments and the specific revisions and corrections of the manuscript are as follows.

[General Comment] – 매우 호의적이지만, 문제점을 지적한 Comment의 경우 (사례 1)

This is an interesting study which investigates an important topic, the prognostic value of ischemia in relationship to vulnerable plaque.
The strengths of the study include its reasonably large size, multicenter nature, and long follow-up.
Some limitations include the retrospective nature, the lack of a larger cohort of patients with FFR<0.80 who were deferred PCI, and most importantly the fact that the primary component of the endpoint was revascularization, while myocardial infarction, a much more interesting endpoint occurred infrequently and was no different between the groups.

[General Comment] – 매우 호의적이지만, 문제점을 지적한 Comment의 경우 (사례 2)

The authors assessed the outcomes with MV PCI vs. IRA-only PCI in patients with STEMI and cardiogenic shock with multivessel disease using data from the KAMIR registry. The authors found that MV PCI was associated with lower mortality and need for repeat revascularization when compared with IRA-only PCI. **The limitations are data from a registry with attended selection bias. However, the results are important.**

Response:

We thank you for all your valuable and positive comments. **We fully understand the potential limitations of the current study and tried our best to address each of the issues raised by the Reviewer.** We hope that these revisions fulfill the Reviewer's comments and the specific revisions and corrections of the manuscript are as follows.

Lee JM, Rhee TM, Hahn JY, JACC 2018;71(8):844-856
Lee JM, Koo BK, JACC 2017;70(17):2114-2123
Lee JM, Koo BK, JACC 2019;21;73(19):2413-2424

Real Example: Response to General Comment

[General Comment] – 호의적이지 않으면서 Critical한 point를 지적한 경우

- This study differs from some prior studies in that FFR was assessed after PCI, and sums the 3 vessel score. Although the results report higher rates of MACE associated with lower three-vessel FFR, **which is not surprising based on prior similar reports**, as shown in table 2, **the difference is exclusively driven by ischemia-driven revascularization. Specifically, cardiac death rates and myocardial infarction are the same between groups.**
- Furthermore, **no information is provided on the medical therapy** relevant to figure 6.
- The important question of whether **abnormal FFR values may provide incremental value** or are **more prognostic than angiographic assessment of stenosis and/or disease burden** for clinical events is not addressed in the study.

Response:

We thank you for this comment. **We agree with the Reviewer's comment regarding the difference in 2-year MACE between high and low 3V-FFR group was mainly driven by higher ischemia-driven revascularization in the low 3V-FFR group (일단 인정할건 인정하고….). However, the median time-to-ischemia driven revascularization was 399.0 days (Q1-Q3: 273.0-634.0) and most lesions showed progression of de novo lesions (하지만, 그게 다가 아님을 살짝 반박). Furthermore, 62.5% of patients with ischemia-driven revascularization presented with acute coronary syndrome. Similarly, the median time-to-revascularization in non-ACS patients was 375.5 days (Q1-Q3 273.0-489.3) (추가 Evidence를 제시함으로써 우리 주장을 더욱 뒷받침.).**

As for the medical treatment, the patients in the current study were closely followed with optimal medical treatment. Statins were used in 87.9% of patients at discharge and 90.4% at 2-year follow-up.

We agree with the Reviewer's comment regarding the importance of incremental value of FFR compared with angiographic lesion severity. However, this additive value had been validated by a previous randomized study and several registries and the limitation of angiographic stenosis in defining ischemia-causing stenosis is also well-known. **This could be also reproduced in our study. When the multivariable model was constructed with incorporating residual per-vessel stenosis severity and final per-vessel FFR values along with patient-level covariates, FFR was an independent predictor for 2-year clinic events (HR 2.81, 95% CI 1.58-4.99, p<0.001), but angiographic % diameter stenosis was not.**

General Comment에서부터 Critical한 문제를 지적한 reviewer는 따라오는 Comment에서 반드시 신랄한 비판을 하는데, General Comment에 대한 답변에서부터, 이 문제에 대해 짚고 넘어가면서 대응을 시작하는 것이 더 좋은 것 같습니다.

Lee JM, Koo BK, Eur Heart J. 2018 Mar 14;39(11):945-951

Real Example: Critical Comment to Fundamental Rational of the Study

[Reviewer #1 - Comment #2]
Clearly minimum lumen area and plaque burden are likely to be associated with a lower FFR.
By including these features**, it is sort of a self-fulfilling prophecy that CCTA HRPC will correlate with FFR.**

[Reviewer #2 - Comment #1]
HRPC- the authors include both stenosis and MLA.
I think this results in model overfitting as these are clearly not independent.

Response:
We thank you for this comment. As the Reviewer pointed out, there are correlations among MLA, plaque burden, and FFR. **However, the anatomic stenosis severity (MLA or plaque burden) showed only modest correlation with FFR, and diagnostic performance (especially positive predictive value) of any anatomical parameter derived from IVUS, OCT, or CCTA was reported consistently to be low in defining functionally significant lesions. Moreover, quantitative lesion severity (MLA or plaque burden) also showed significant association with qualitative plaque characteristics in previous invasive imaging studies, and both quantitative and qualitative plaque characteristics were independent predictors of future clinical events in invasive imaging studies (PROSPECT, ATHEROREMO-IVUS, and VIVA).**
Taken together, these results suggest that quantitative lesion severity, qualitative plaque characteristics, and physiologic stenosis severity are inter-related, and all these individual parameters possess prognostic significance. However, those relationships can differ in each patient/lesion due to numerous patient- or lesion-specific parameters such as plaque contents, presence of positive or negative remodeling, lesion location, or variation in coronary flow and microvascular function. **Nevertheless, none of the previous studies evaluated the prognostic implications from integrated information of quantitative lesion severity, qualitative plaque characteristics, and physiologic lesion severity.**
Therefore, this study was performed to investigate the association of quantitative and qualitative plaque characteristics assessed by CCTA and physiologic lesion severity defined by FFR, and prognostic implications of CCTA-defined HRPC according to FFR in CAD patients. In this regard, we defined HRPC as a combination of 6 parameters (MLA, plaque burden, low-attenuation plaque, positive remodeling, napkin-ring sign, or spotty calcification). **We added the above points and modified the Discussion section, as follows.**

In the Discussion section (page 18, line 4):
Previo… those
relation… lesion
locatio…
It is we… s have
not be… tantly,
wheth… oal of
revasc…

연구에서 사용했던 Major classification의 Definition에서부터 문제가 있지 않느냐는 지적으로, 이 Comment에 대한 대응은 연구의 fundamental rationale를 결정하는 것이기 때문에 반드시 조목조목 우리의 rationale를 설명하고, Discussion에서도 이러한 주장에 대한 뒷받침 문장을 추가로 서술해야 agree 시킬 수 있다고 생각했습니다.

Lee JM, Koo BK, JACC 2019;21;73(19):2413-2424

Real Example: Fully compliant with Reviewer's request

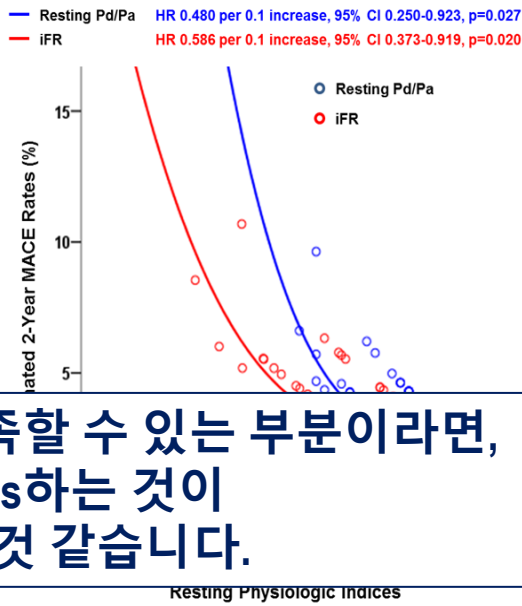
[Comment #4]
Figure 3 **should be** adapted in a similar manner **by performing the analysis on a per patient basis**. I have presumed that lines are derived from a simple Cox PH model with the physiologic indices as a quantitative parameter. It is unclear what the circles represent? At the lesion level, MACE has or hasn't occurred. Do the graphs represent 2-year event rates? What is the unit for the Hazard ratios? Is it per %, per 10% or per 100%?

Response:
We thank you for this comment which was well taken by the authors. **Figure 3 was re-drawn using per-patient data.** The lines were derived from the univariable Cox regression model with the physiologic indices as a continuous value. The red and blue circles represent each patient's iFR and resting Pd/Pa values, and estimated MACE rates according to the iFR or resting Pd/Pa values, respectively. The Y axis presents estimated 2-year MACE rates and the unit of hazard ratio and 95% confidence intervals are per 0.1 increase of each physiologic index. We further specified these in the Figure legends and in Figure 3 as follows.

Figure Legends (page 25, line 1):
Figure 3. Associations Between Estimated MACE Rates and Resting Physiologic Indices
The association between 2-year major adverse cardiac events (MACE) and resting Pd/Pa or iFR was evaluated. Both indices showed significant association with 2-year MACE risk as continuous values. Red and blue lines represent regression lines for iFR and resting Pd/Pa as continuous values, respectively. Red and blue circles represent each patient's iFR and resting Pd/Pa values and estimated MACE rates according to the iFR or resting Pd/Pa values, respectively.
Abbreviations: HR, hazard ratio; CI, confidence intervals; others are as with Figure 1.

In addition, the Results section was also changed accordingly, as follows.
In the Results section (page 15, line 5):
Both resting Pd/Pa and iFR as continuous values showed significant association with

Figure 3. Associations Between Estimated MACE Rates and Resting Physiologic Indices



**Reviewer의 요청에 대해 가진 자료로 충분히 충족할 수 있는 부분이라면,
200% 만족할 수 있도록 Fully address하는 것이
조금이라도 가능성을 높이는 길 인 것 같습니다.**

Lee JM, Koo BK, JACC 2017;70(17):2114-2123

Real Example: Fully compliant with Editor's request

<< Associate Editors' Comments for the Author >>
[Comment #1]
A comment should be added in the Discussion section regarding the recent German study (Thiele et al.) on the same study.

Response:
We thank you for all your valuable and positive comments. **We absolutely agree with the Associate Editor's opinion regarding the CULPRIT-SHOCK trial.**
Although differences in study population and in study design preclude a direct comparison of the results, differences in the results between the CULPRIT-SHOCK trial and the current study, derived from the nationwide multicenter dedicated registry for AMI, might be interpreted in the following context. **First,** the overall incidence of all-cause death at 30 days was much higher in the CULPRIT-SHOCK trial than the current study (47.4% vs. 21.9%). However, the use of mechanical support was similar between the 2 studies (28.2% vs. 26.7%), suggesting that substantial patients enrolled in the CULPRIT-SHOCK trial died without mechanical support. **Second,** in the CULPRIT-SHOCK trial, 17.7% of patients in the IRA-only PCI group (61/344 patients) underwent staged multivessel revascularization and 12.5% of patients in the IRA-only PCI group (43/344 patients) underwent immediate multivessel revascularization. Overall, 30.2% of patients in the IRA-only PCI group (104/344 patients) were actually

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리뷰어 모두 accept라도 결국 Editor가 싫으면 안 되는 것 같습니다.

not possible, we thoroughly described the abovementioned differences in the Discussion section, as follows.

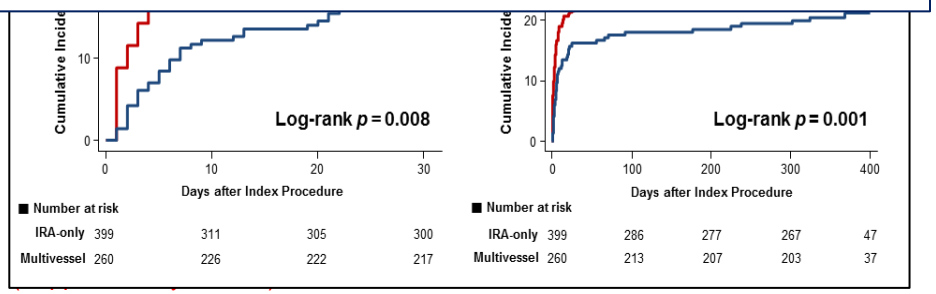
In the Discussion section (page 18, line 11):
Recently, the CULPRIT-SHOCK trial reported 30-day clinical outcomes of 685 STEMI patients with multivessel disease and cardiogenic shock who were randomly allocated into angiography-guided immediate multivessel PCI or IRA-only PCI group. 중략….
(1페이지 반에 걸쳐 address했습니다.)

<< Associate Editors' Comments for the Author >>
[Comment #2]
An effort should be made to provide **30-day data** and also **new dialysis rates at 30 days and 1 year.**

Supplementary Table 2. Comparison of 30-day outcomes according to treatment strategy (Abbreviated)

	Multivessel PCI (N = 260)	IRA-only PCI (N = 399)	Unadjusted HR (95% CI)	*P*	Multivariable-adjusted HR (95% CI)	*P*
All-cause death	16.5% (43)	26.1% (101)	0.61 (0.43-0.88)	0.007	0.54 (0.37-0.78)	0.001
Cardiac death	14.3% (37)	24.5% (94)	0.57 (0.39-0.83)	0.004	0.48 (0.32-0.72)	<0.001
Recurrent MI	0.8% (2)	0.3% (1)	2.88 (0.26-31.8)	0.388	2.08 (0.04-109.6)	0.717
Any repeat revascularization	0.9% (2)	1.3% (4)	0.69 (0.13-3.77)	0.670	0.13 (0.01-1.59)	0.112
Non-IRA repeat revascularization	0.4% (1)	1.0% (3)	0.46 (0.05-4.42)	0.500	0.07 (0.00-2.31)	0.133
Definite or probable stent thrombosis	0.0% (0)	0.0% (0)	-	-		
Death or MI	17.3% (45)	25.8% (101)	0.65 (0.45-0.92)	0.014	0.57 (0.39-0.82)	0.003
Death or new RRT	18.1% (45)	27.0% (103)	0.63 (0.44-0.89)	0.010	0.55 (0.38-0.80)	0.002
Patient-oriented composite outcome*	17.7% (46)	26.6% (104)	0.64 (0.45-0.91)	0.012	0.56 (0.39-0.81)	0.002

Supplementary Figure 1. Risk of All-Cause Death or New Renal Replacement Therapy, According to Treatment Strategy



Lee JM, Rhee TM, Hahn JY, JACC 2018;71(8):844-856

Real Example: 대응은 언제나 조금 과한 정도로..

[Comment #4]
The use of offline IFR calculation sending data to a Core Lab for analysis is **unusual**, mentioned both in the methods and in the patient section. **Do the authors believe this had any contribution to change in data and value of IFR given the current sensitivity of the IFR measurement to artifact of EKG quality?**

Response:
We thank you for this comment. In this study, all iFR values were calculated from the core laboratory in the Imperial College, London, where the concept of iFR was developed. Nevertheless, we acknowledged the potential limitation of off-line calculation of iFR. **In order to fulfill the Reviewer's comment, we added this to the Limitations section as follows.**

In the Limitations section (page 18, line 22):
Fourth, iFR was calculated off line in the independent core laboratory using the resting pressure tracing data.

이 코멘트의 경우 아주 critical 하거나, skeptical 하지는 않지만, 논문에 사용한 주요 parameter의 신뢰성에 대해 묻는 것이기 때문에, 리뷰어를 만족시키기 위해서는 조금 더 과하게 대응하여 Limitation까지 추가하는 모습을 보여야 한다고 생각했습니다.

Lee JM, Koo BK, JACC 2017;70(17):2114-2123

Real Example: 적절한 지적에 대해서는 Cool하게..

[Comment #2]
Do you think it is appropriate to say FFR was validate with PET? With such a tiny number of stenoses? Stenosis all in a non-clinical distribution (very severe, and very mild).
Maybe it would be fairer to say "assessed" or "compared"

Response:
This is an excellent comment, which was appreciated by the authors. As recommended, we changed the expression as follows.

In the Introduction section (page 7, line 16):
[Before]
Previously, Uren et al. demonstrated the relationship between coronary stenosis severity and the degree of blood flow impairment in humans using PET, and De Bruyne et al. **validated** the concept of FFR using PET parameter.

[After]
Previously, Uren et al. demonstrated the relationship between coronary stenosis severity and the degree of blood flow impairment in humans using PET, and De Bruyne et al. **assessed** the concept of FFR using PET parameter.

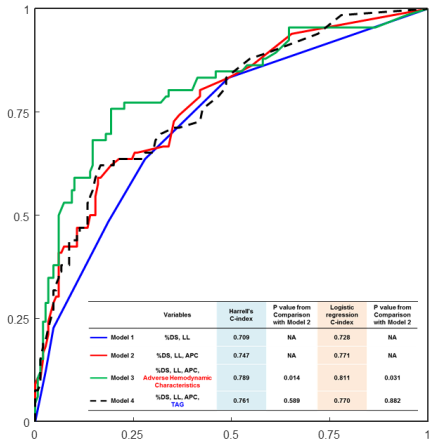
Lee JM, Koo BK, Circulation.2017;136(19):1798-1808

Real Example: 논문의 흐름에 맞지 않는 요구

[Comment #8]
Please present data on coronary transluminal attenuation gradient (TAG). For example, how does Model 1 + TAG + APC perform.

Response:
We thank you for this comment. In order to address the Reviewer's comment, we analyzed the TAG and compared the discrimination ability of models as presented in **Reviewer Only Figure 1.**

Reviewer Only Figure 1. Comparison of discrimination ability among various models.



	Variables	Harrell's C-index	P value from Comparison with Model 2	Logistic regression C-index	P value from Comparison with Model 2
Model 1	%DS, LL	0.709	NA	0.728	NA
Model 2	%DS, LL, APC	0.747	NA	0.771	NA
Model 3	%DS, LL, APC, Adverse Hemodynamic Characteristics	0.789	0.014	0.811	0.031
Model 4	%DS, LL, APC, TAG	0.761	0.589	0.770	0.882

As you can see from the results, Model with %DS, lesion length, APC, and **TAG** showed **significantly lower C-index**, compared with any Models with %DS, lesion length, APC, and **hemodynamic parameters.** In addition, Models with TAG did not show any significant difference in discrimination ability, compared with Model 2. **We could not include the above result in the manuscript due to the limitation of word count. We had to reduce the number of the words according to the editor's recommendation.**

**도저히 논문의 흐름상 끼워 넣을 수 없는 Irrelevant한 요구에 대해서
그냥 못하겠다. 데이터가 없다. 라고 대응하는 것보다는
간단한 노력으로 얻을 수 있는 데이터를 Reviewer only figure로 제시하였습니다.**

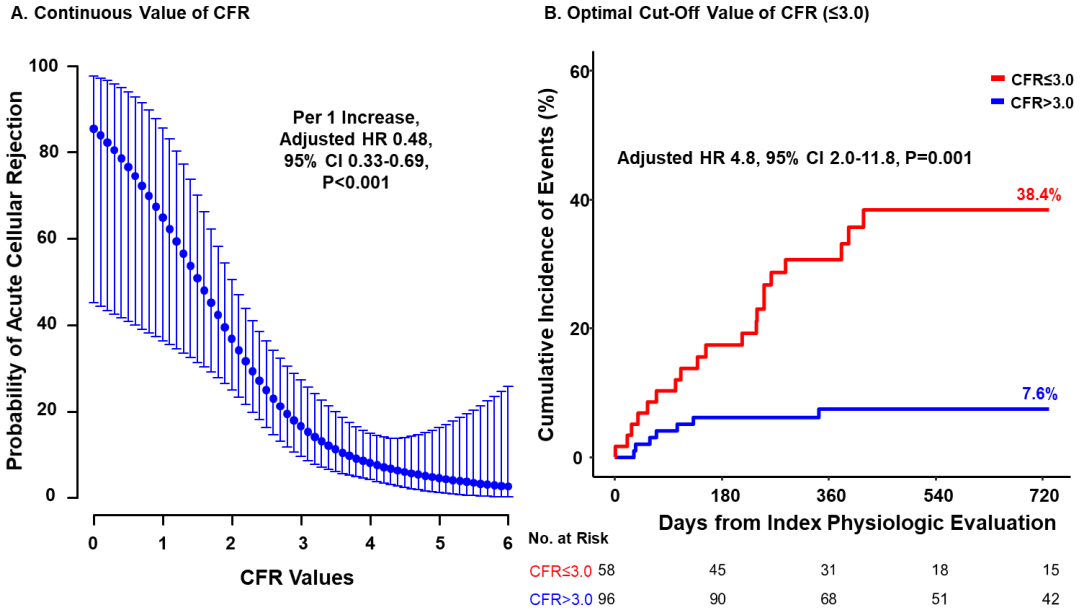
Lee JM et al. JACC Cardiovasc Imaging 2019;12(6):1032-1043

Real Example: 나쁘지 않은 지적이지만, 논문 흐름에 불편한 경우

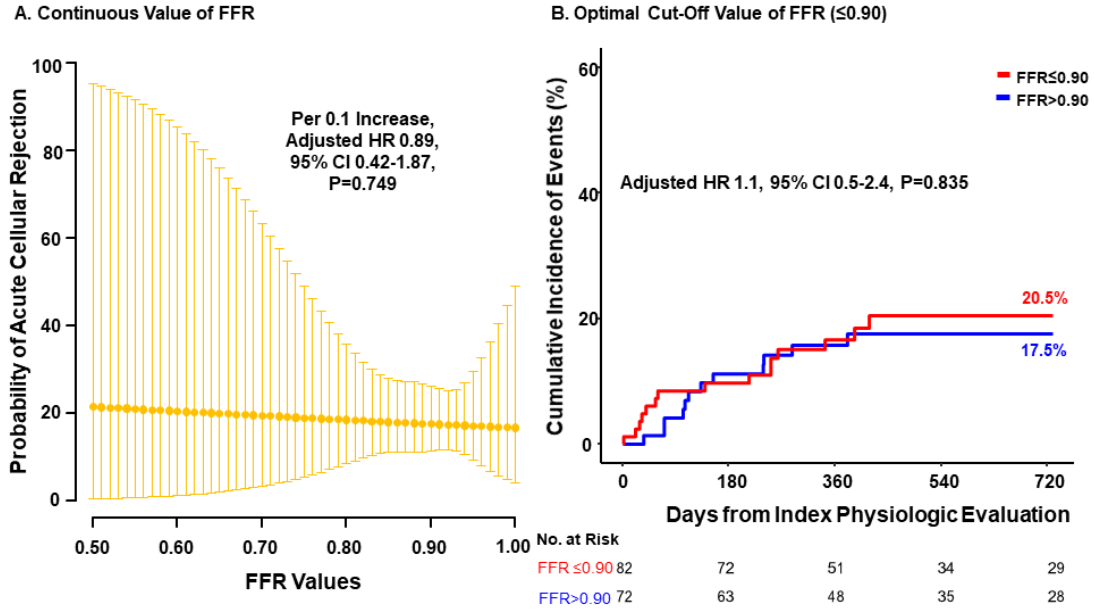
[Comment #5]
Results from CFR and FFR should also be included.

Response:
We appreciate this comment. **When coronary microcirculatory dysfunction was defined by CFR and its optimal cut-off value, similar results were observed**, and patients with CFR≤3.0 showed increased risk of acute cellular rejection compared to those with CFR>3.0 (adjusted HR 4.8, 95% CI 2.0-11.8, P=0.001) (**Supplementary Figure 2 and Supplementary Table 1**). **Conversely, FFR was not predictive of acute cellular rejection** (**Supplementary Figure 3 and Supplementary Table 2**). These results were added in the Results section, **Supplementary Figures 2 and 3, and Supplementary Tables 1 and 2**, as follows.

Supplementary Figure 2. CFR and Risk of Acute Cellular Rejection



Supplementary Figure 3. FFR and Risk of Acute Cellular Rejection



Lee JM et al. Circulation. 2021 Nov 2;144(18):1459-1472.

Real Example: Reviewer의 요구를 들어주기 싫을 때 완곡한 거절

[Comment #12]
The authors **should** include the individual endpoints (death, MI and revascularization) and their percentages in the text of the results and not just as a table.

Response:
We thank you for this comment. **However, we had to limit the total word count within 5000 words and are not allowed to lengthen the revised manuscript due to the recommendation from the Editor. Furthermore, the editorial office recommended to remove the numbers from the main manuscript already provided in the tables (수용할 수 없는 것에 대한 사유를 남의 탓을 하면서 완곡하게 거절..).**

Although we respect the Reviewer's comment, we could not add more numbers in the revised manuscript. However, if the Reviewer still wants to add the individual endpoints and their percentages in the text, we would be happy to do that in a revised manuscript.
(하지만, 우리는 "정" 이기 때문에 늘 빠져나갈 여지를 두어야 합니다..)

논문의 Contents에 대한 Critical한 comment가 아니면서, 단순히 툭 던지는 식의 요구인데, 이를 받아들일 경우 오히려 논문이 복잡해지고, 도움이 되지 않는다고 판단하여 거절했습니다. 하지만, 재차 요구할 경우 받아들이겠다고 서술했습니다.
(아마 99%의 사람은 인간인 이상 또 요구하지 않을 것 같습니다.)

Lee JM, Koo BK, JACC 2019;21;73(19):2413-2424

Real Example: 논문의 Integrity유지를 위해 도저히 받아들일 수 없는 요구일 때

[Comment #1]

HRPC- the authors include both stenosis and MLA. I think this results in model overfitting as these are clearly not independent.

[Comment #2]

The relationship between HRPC and FFR is interesting but **why not remove stenosis and MLA and focus only on plaque features?**

Response:

We thank you for this comment. As the Reviewer pointed out, there are correlations among MLA, plaque burden, and FFR. However, the anatomic stenosis severity (MLA or plaque burden) showed only modest correlation with FFR, and diagnostic performance (especially positive predictive value) of any anatomical parameter derived from IVUS, OCT, or CCTA was reported consistently to be low in defining functionally significant lesions. Moreover, quantitative lesion severity (MLA or plaque burden) also showed significant association with qualitative plaque characteristics in previous invasive imaging studies, and both quantitative and qualitative plaque characteristics were independent predictors of future clinical events in invasive imaging studies (PROSPECT, ATHEROREMO-IVUS, and VIVA). Taken together, these results suggest that quantitative lesion severity, qualitative plaque characteristics, and physiologic stenosis severity are inter-related, and all these individual parameters possess prognostic significance. However, those relationships can differ in each patient/lesion due to numerous patient- or lesion-specific parameters such as plaque contents, presence of positive or negative remodeling, lesion location, or variation in coronary flow and microvascular function. Nevertheless, none of the previous studies evaluated the prognostic implications from integrated information of quantitative lesion severity, qualitative plaque characteristics, and physiologic lesion severity. Therefore, this study was performed to investigate the association of quantitative and qualitative plaque characteristics assessed by CCTA and physiologic lesion severity defined by FFR, and prognostic implications of CCTA-defined HRPC according to FFR in CAD patients. In this regard, we defined HRPC as a combination of 6 parameters (MLA, plaque burden, low-attenuation plaque, positive remodeling, napkin-ring sign, or spotty calcification). We added the above points and modified the Discussion section, as follows.

In the Discussion section (page 18, line 4):

Previous studies showed that there are associations among quantitative lesion severity, qualitative plaque characteristics, and physiologic lesion severity.(1-6) (이후 생략)

Response:

We thank you for this comment. Previous studies showed that both quantitative and qualitative components need to be considered to define HRPC for the prediction of future adverse events and the clinical relevance of the number of HRPC (Please refer to the response to Comment #1 as well.).

In this regard, we defined HRPC as a combination of 6 parameters (MLA, plaque burden, low-attenuation plaque, positive remodeling, napkin-ring sign, or spotty calcification).

Furthermore, even after the removal of MLA and PB from the calculation of number of HRPC, a significant association was observed between FFR and number of HRPC ($p<0.001$), and number of HRPC was significantly different among classification by FFR (overall p value <0.001).

논문의 틀을 유지하기 위해 받아들일 수 없는 comment의 경우에 라도, 리뷰어의 요구에 따라 변화를 주었을 때에도 overall result가 바뀌지 않는 다는 것을 간단하게 제시하고, 우리의 Rationale를 서술..

Lee JM, Koo BK, JACC 2019;21;73(19):2413-2424

Real Example: Reviewer의 지적이 학문적으로 틀린 경우

[Comment #10]
The many subgroups analyses performed suffers from multiple testing. No correction is performed for multiple testing.

Response:
We thank you for this constructive comment and agree with the Reviewer's concern regarding subgroup analysis. We also fully acknowledged the issue regarding multiple testing, therefore, we did not present the individual p values in each subgroup presented in Figure 4. The main purpose of the subgroup analysis was to evaluate the interaction p value in order to explore the potentially different clinical impact of multivessel PCI across various subgroups. As you well know, adjustment of multiple testing is not applicable to interpret "interaction p value".
However, we are willing to move Figure 4 to the Supplementary Appendix if the Reviewer thinks this would be appropriate.

In addition, we further specified that the results of exploratory subgroup analysis should be interpreted in the context of significant interaction p value in the Figure Legends section, as follows. We appreciate this comment from the Reviewer.

이 리뷰어는 Interaction P value의 개념을 모르는 사람입니다.
그럼에도 불구하고 리뷰어를 자극하지 않으면서도, 완곡하게 "As you well know…"등의 문구를 통해 당신도 잘 알겠지만, 사실은 ~~~ 인 것이다 라고 돌려서 지적을 해주고,
틀린 지적이라도, 리뷰어가 원할만한 것에 대해 미리 대응을 하는 것이 유리합니다.
우리는 "정"이고, "갑"인 리뷰어가 혹시라도 불쾌할지 모르므로,
저는 이런 경우 꼭 고맙다는 인사를 다시 씁니다.

Lee JM, Rhee TM, Hahn JY, JACC 2018;71(8):844-856

Real Example: RCT가 아닌 연구에 대한 리뷰어의 형식적인 지적

[Comment #2]
How did the authors arrive at a sample size of 100 AMI patients and 203 stable patients? **Did they perform a power calculation to determine these sample sizes?**

Response:
We thank you for this comment. **The primary purpose of the current study** was to compare the changes of FFR or iFR between SIHD and non-culprit vessel of AMI patients with any given stenosis severity levels using historical data of prospective registries. Therefore, we calculated statistical power to compare mean values of FFR or iFR between SIHD and non-culprit vessel of AMI patients to test whether FFR or iFR would underestimate or overestimate lesion severity in non-culprit vessel of AMI, respectively, compared with those of SIHD patients. **Given the diameter stenosis and lesion length adjusted mean and standard deviations, the current sample size would provide 61% statistical power for FFR and 89% statistical power for iFR as one-sided test.**

Non-randomized study에 대해 간혹 Sample size를 계산했는지에 대한 지적이 있습니다.
이 경우 current sample size가 제공할 수 있는 statistical power를 제시하시면 됩니다.

Choi KH, Lee JM, JACC Intervention 2018;11(18):1848-1858

Real Example: .

Reviewer의 요구를 들어주기에는 현실적인 제약이 있는 경우 #1

[Comment #5]
What was the indication for multivessel PCI?

Response:
We thank you for this constructive comment. **As the current study was a non-randomized study, the decision for performing non-IRA PCI was based on the operator's discretion. We fully acknowledge that this is major limitation of the current study, and described in the Limitations section, as follows.**

In the Limitations section (page 20, line 20):
Fourth, although clinical outcomes according to completeness of revascularization were presented, the decision regarding the revascularization timing, extent, and completeness was left to the operator's discretion.

Registry Data에서 조사하지 않았고, 또 조사하기에는 현실적인 제약이 너무 많아 불가능하다고 판단되는 경우는 자세하게 쓸 필요 없이 Cool하게 제한점으로 인정하는 것이 더 현명한 방법인 것 같습니다.

Lee JM, Rhee TM, Hahn JY, JACC 2018;71(8):844-856

Real Example: .
Reviewer의 요구를 들어주기에는 현실적인 제약이 있는 경우 #2

[Comment #8]
Overall, the study would be stronger if the patients had non-invasive perfusion imaging to go along with the invasive physiology. Perhaps at least some of them have this data and if so, it should be reported.

Response:
We thank you for this constructive comment, and we fully agree with your opinion. **Unfortunately, the results of non-invasive test were not systematically performed in our study.** We've searched the data on non-invasive tests, especially myocardial perfusion imaging (SPECT or PET) and found that none of Group D patients underwent non-invasive myocardial perfusion imaging. **However, even with the results of non-invasive tests, it would not be easy to clearly link the association between those and invasive physiologic indices. It is well-known that non-invasive tests have limitations in defining the presence of myocardial ischemia, especially in patients with multivessel disease.** **However, we fully acknowledge this is one of limitations of the current study, which was presented in the Limitations section as follows.**

In the Limitation section (page 22, line 15):
In addition, the results of non-invasive tests were not available in our study. Even though the validated physiologic indices indicated the presence or absence of myocardial ischemia, this relationship could not be reaffirmed by non-invasive test results.

Registry Data에서 조사하지 않았고, 또 조사하기에는 현실적인 제약이 너무 많아 불가능하다고 판단되는 경우이나, 리뷰어의 분위기상 치명적인 약점으로 인지될 comment의 경우는 위처럼, 설령 요구하는 정보가 있었다고 하더라도,
현재의 결과가 크게 바뀌지 않을 것이며, 때문에 요구하는 정보가 없는 것이
Critical weakness는 아님을 간접적으로라도 쓰는 것이 나을 것 같습니다.

Lee JM, Koo BK, JACC 2016;67(10):1158-1169

Real Example: .
다른 그룹의 Rebuttal letter…..

1. 연구에 사용한 index의 benefit이 없다고 생각한다.
Response: This comment falls out of the scope of our research, and therefore we kindly believe it does not worth discussion in the manuscript or the rebuttal letter.

2. 연구에 사용한 index자체가 틀렸다.
Response: This comment falls out of the scope of our research, and therefore we kindly believe it does not worth discussion in the manuscript or the rebuttal letter.

3. 이 연구에서 Relevance한 메시지를 얻기는 불가능하다고 생각한다.
Response: We believe that this is perfectly possible, and is supported by published research performed by other authors and quoted as part of the discussion of our findings.

4. Scientific design이 flawed 하다
Response: The comment of the reviewer might have been relevant at the time of submission of the original trials, but not now that have already been published. Overall, this comment falls out of the scope of our research, and therefore we kindly believe it does not worth discussion in the manuscript or the rebuttal letter.

**출처를 밝힐 수는 없지만, 저는 개인적으로,
이 리뷰어의 지적과 이 지적에 대한 저자들의 대응을 보면서
학자로서의 길과 너무 멀어진 것이 아닌가 생각했습니다.**

**"Peer Review"는 말 그대로, "동료/친구/동반자"와의 communication이기 때문에
예의를 갖출 줄 아는 사람이 되어야 한다고 생각합니다.**

Summary

- **Revision Process는 Reviewer와의 Communication**
- 따라서 우리의 주장이 다양한 경우에 있어서도 동일한 결과를 보인다는 것을 증명해야 함
  ➔ **Sensitivity Analysis 를 잘 활용해야 합니다.**
- 대응이 가능한 Comment는 100%만족할 수 있도록 최선을 다해서 대응
- 대응이 가능하지만, 논문의 Main result로는 흐름이 맞지 않을 때에는 Supplementary Appendix 를 적극적으로 활용합니다.
- 대응이 가능하지만, 논문의 Integrity를 해칠 수 있는 comment는 왜 Reviewer의 요구를 100% 수용할 수 없는지에 대해 조목조목 서술을 함으로써, Reviewer를 설득해야 합니다. 또한 이 경우 Reviewer Only Figure/Table을 활용하여 요구는 수용하되, 논문의 Integrity를 해치지 않는 범위에서 대응합니다.
- 대응이 불가능한 경우, 대응을 하기 위해 소요되는 시간/노력/자금/연구팀의 여력을 냉철하게 계산하여 추가 조사할 것인지, Limitation에 기술하고 끝낼지 판단해야 합니다.
- **마지막으로 어떤 경우에도 타인에 대한 예의를 갖추어야 한다고 생각합니다.**
  (우리가 리뷰어 일 때나, 리뷰를 받는 입장일 때나...)

Thank You For Your Attention !

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If you have any question, don't hesitate to e-mail me.

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