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Mannheim, 12<sup>th</sup> of October 2018

Dear Dr. Ya-Juan Ma,

Thank you for the favorable evaluation of our article entitled **“Instantaneous wave-free ratio (iFR<sup>®</sup>) to determine hemodynamically significant coronary stenosis - a comprehensive review“**.

Based on the thoughtful comments our work has received, we have revised the manuscript and are thus resubmitting our contribution for de-novo evaluation. Please find enclosed our detailed responses to the reviewer. We believe that our article meets the high standards and innovative scope of your journal and will be of great interest to readers.

Sincerely yours,

Stefan Baumann, MD

Dirk Lossnitzer, MD



**Editor:**

We thank the editor for his recommendation and changed the following aspects.

- Please offer point to point answer to all reviewers.

We changed the manuscript type from “REVIEW” to “MINIREVIEW” and added the “**Manuscript NO: 41709**”. Furthermore, we responded to all reviewers and mentioned the changes in this rebuttal letter below.

- A short running title should be than 6 words. Please correct it.

We changed “~~Instantaneous wave-free ratio (iFR<sup>®</sup>) to determine hemodynamically significant coronary stenosis a comprehensive review~~” to “iFR<sup>®</sup> to determine coronary stenosis significance”

- Please offer the audio core tip

We recorded the audio core tip and will upload it accordingly.

Further changes to meet the requirements by BPG for a MINIREVIEW:

We added the following paragraph for Open-access to meet the requirements for a MINIREVIEW:

“**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>”

We added following information to meet the requirements by BPG for a MINIREVIEW:

“**Received:** August 25, 2018

**Peer-review started:** August 25, 2018

**First decision:** October 10, 2018

**Revised:**

**Accepted:**

**Article in press:**

**Published online:”**

We added the following copyright statement to meet the requirements by BPG for a MINIREVIEW: “©

**The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.”

Furthermore, we added page numbers.



**Reviewer #1 (ID: 00397579):** Baumann et al comprehensively reviewed the available literature on iFR in CAD assessment. It is well written and a good piece of addition to the literature. The manuscript has focused on the basic principles and clinical studies justifying iFR in clinical application.

We thank the reviewer for his valuable evaluation. We addressed his recommendations and made the following changes.

It would be very helpful and informative if the authors could spend a paragraph or two to illustrate existing controversies on iFR and its clinical application, as well as factors might affect the accuracy or consistency of iFR measurement, such as myocardial contractility, LVEDP, arrhythmia and microvascular disease etc.

We added the following two paragraphs to "LIMITATIONS" including respective references:

"High incidents of patient related discomfort, like dyspnea, chest pain, hypotension and AV-blocks or in one recorded case even ventricular fibrillation<sup>[33]</sup> still remain a limitation of the application of Adenosine<sup>[34]</sup> which can be overcome by an Adenosine free assessment like the iFR<sup>®</sup>."

33 **Buccheri D**, Sorce S, Piraino D, Andolina G. Fractional flow reserve: A useful tool for interventionists which should be used with caution! *Int J Cardiol* 2016; **221**: 404-405 [PMID: 27404714 DOI: 10.1016/j.ijcard.2016.06.303]

34 **Gotberg M**, Cook CM, Sen S, Nijjer S, Escaned J, Davies JE. The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve. *J Am Coll Cardiol* 2017; **70**(11): 1379-1402 [PMID: 28882237 DOI: 10.1016/j.jacc.2017.07.770]

"Regarding microvascular diseases, studies could not prove a correlation between FFR and the index of microvasculature resistance (IMR), an index for the microvascular status, measured by the thermodilution technique<sup>[35]</sup>. This must not be seen as a shortcoming of the FFR method since it might rather show that micro- and macrovascular diseases are caused by different disease processes<sup>[36]</sup>. These findings can be employed on iFR<sup>®</sup>, since its non-inferiority towards FFR was proven."

35 **Lee JM**, Layland J, Jung JH, Lee HJ, Echavarría-Pinto M, Watkins S, Yong AS, Doh JH, Nam CW, Shin ES, Koo BK, Ng MK, Escaned J, Fearon WF, Oldroyd KG. Integrated physiologic assessment of ischemic heart disease in real-world practice using index of microcirculatory resistance and fractional flow reserve: insights from the International Index of Microcirculatory Resistance Registry. *Circ Cardiovasc Interv* 2015; **8**(11): e002857 [PMID: 26499500 DOI: 10.1161/CIRCINTERVENTIONS.115.002857]

36 **Yong AS**, Ho M, Shah MG, Ng MK, Fearon WF. Coronary microcirculatory resistance is independent of epicardial stenosis. *Circ Cardiovasc Interv* 2012; **5**(1): 103-108, S101-102 [PMID: 22298800 DOI: 10.1161/CIRCINTERVENTIONS.111.966556]

**Please note:** Due to the additional reference the numbered order of references has changed, therefore the numbering of the following respective references differs from the original submitted article.



Some minor issues:

- page 5, para 2, "little vessels" - non-medical term, should be changed to microvasculature (similar issues below)

We replaced "little vessels", "little blood vessels" and "blood vessels" by "microvasculature" respectively.

- Page 5, para 3: "very scarce" - inaccurate description. please change to actually reported utilization rates such as 10% in some reference

We followed the reviewer's advice and deleted "its use in clinical practice is very scarce" and added following information: "it is only used in about 6% of patients undergoing PCI for intermediate coronary stenoses (40-70% diameter stenosis)"

- page 5, para 3. in discussion of shortfalls of FFR, the adverse effects of adenosine, such as exacerbation of asthma, causing chest pressure and discomfort, and also transient heart block, hypotension etc should be mentioned.

We kindly refer to p.5 paragraph 3, where we addressed the adverse effects of Adenosine. With respect to the reviewers valuable recommendation we added ", chest pressure and discomfort, hypotension", upgrading the informative content at this point.

- page 8, last para: typo "thereupon"?

We deleted "Thereupon" and changed "the" to "The".

- page 8, typo in subtitle "IFR", need to use "iFR" as a commonly accepted term

We replaced "IFR<sup>®</sup>-" by "iFR<sup>®</sup>-".

- please quote recent meta-analysis in Circ - CVI (de Rosa et al 2018) as well as Van't Veer et al JACC 2017 VERIFY2 study

With respect to the reviewer's recommendation, we added the suggested references by adding following two paragraphs to "INTRODUCTION" and "FURTHER IMPROVEMENTS" including the respective references:

"Next to the two large multicenter studies DEFINE-FLAIR<sup>[19]</sup> and SWEDEHEART<sup>[20]</sup>, which proved the non-inferiority of iFR<sup>®</sup> towards FFR, the first meta-analysis with 23 studies including 6300 coronary lesions was just recently published. This study verified a significant correlation between iFR<sup>®</sup> and the goldstandard FFR and a good performance of iFR<sup>®</sup> identifying FFR-positive stenoses<sup>[21]</sup>."



- 19 **Davies JE**, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Harle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbada RK, Patel MR, Serruys P, Escaned J. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med* 2017; **376**(19): 1824-1834 [PMID: 28317458 DOI: 10.1056/NEJMoa1700445]
- 20 **Gotberg M**, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Ohagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Todt T, Venetsanos D, James SK, Karegren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Frobert O, i FRIS. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med* 2017; **376**(19): 1813-1823 [PMID: 28317438 DOI: 10.1056/NEJMoa1616540]
- 21 **De Rosa S**, Polimeni A, Petraco R, Davies JE, Indolfi C. Diagnostic Performance of the Instantaneous Wave-Free Ratio: Comparison With Fractional Flow Reserve. *Circ Cardiovasc Interv* 2018; **11**(1): e004613 [PMID: 29326150 DOI: 10.1161/CIRCINTERVENTIONS.116.004613]

“Other diastolic resting indices like the diastolic pressure ratio (dPR) obtained in different phases of the diastole like  $dPR_{25-75}$  (25% to 75% of diastole) or  $dPR_{mid}$  (midpoint of diastole) along with Matlab calculated  $iFR^{\circledast}$  ( $iFR_{matlab}$ ) and  $iFR^{\circledast}$ -like indexes shortening the length of the wave-free period by 50 and 100 ms ( $iFR_{-50ms}$  and  $iFR_{-100ms}$ ) were compared to the  $iFR^{\circledast}$  and found to be numerically identical. Therefore, all guidelines and cut-off values as well as clinical recommendation can be applied to these indices<sup>[27]</sup>.”

- 27 **Van't Veer M**, Pijls NHJ, Hennigan B, Watkins S, Ali ZA, De Bruyne B, Zimmermann FM, van Nunen LX, Barbato E, Berry C, Oldroyd KG. Comparison of Different Diastolic Resting Indexes to  $iFR$ : Are They All Equal? *J Am Coll Cardiol* 2017; **70**(25): 3088-3096 [PMID: 29268922 DOI: 10.1016/j.jacc.2017.10.066]

**Please note:** Due to the additional references the numbered order of references has changed, therefore the numbering of the following respective references differs from the original submitted article.

**Reviewer #2 (ID: 00214240):** Excellent overview a example of consecutive lesions would be nice do demonstrate an advantage of IFR over FFR in the mean time the guidelines were changed and IFR is also a class I indication.

We thank the reviewer for his valuable recommendation. We addressed his comment and added the following sentence to “INTRODUCTION” and “CONCLUSION AND FUTURE PERSPECTIVES” including the corresponding reference: “Besides FFR,  $iFR^{\circledast}$  was just recently adopted as a Class-IA-recommendation in the ECS/EACTS guidelines of 2018 on myocardial revascularization<sup>[22]</sup>.”

- 22 **Neumann FJ**, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, Group ESCSD. 2018 ESC/EACTS



Guidelines on myocardial revascularization. *Eur Heart J* 2018 [PMID: 30165437 DOI: 10.1093/eurheartj/ehy394]

Furthermore, in the “Abstract”, the “Core tip”, the “INTRODUCTION” and the “CONCLUSION AND FUTURE PERSPECTIVES” we added “initially” to the following sentences to express that FFR was the first method to be adopted as a Class-IA-recommendation in the ECS/EACTS guidelines of 2014 on myocardial revascularization:

“The FFR-guided revascularization strategy has been initially classified as a Class-IA-recommendation in the 2014 ESC/EACTS guidelines on myocardial revascularization.”,

“Invasive fractional flow reserve (FFR) measurement ... has been initially classified as a Class-IA-recommendation in the 2014 ESC/EACTS guidelines on myocardial revascularization.”,

“This was initially adopted as a ~~class-IA-recommendation~~ Class-IA-recommendation in the ECS/EACTS guidelines of 2014 on myocardial revascularization<sup>[5]</sup>.” and

The current standard of cardiac invasive ischemic diagnostic is invasive FFR-measurement, which was initially adopted as a ~~class-IA-recommendation~~ Class-IA-recommendation to the ECS/EACTS guidelines of 2014 on myocardial revascularization.”.

We consequently deleted the following sentence in “CONCLUSION AND FUTURE PERSPECTIVES”  
“Based on the current published data the iFR<sup>®</sup>-method has the potential to be adopted to the future guidelines of myocardial revascularization.”

**Please note:** Due to the additional reference the numbered order of references has changed, therefore the numbering of the following respective references differs from the original submitted article.

**Reviewer #3 (ID: 02636166):** The authors made a comprehensive review on the application of iFR for CAD stenoses. The paper was well written. Only a few grammar errors were present. Please correct them before acceptance. Best

We thank the reviewer for his valuable recommendation. Ms. Elizaveta Skarga, the 3<sup>rd</sup> coauthor and a native speaker carefully revised the language of our manuscript again. She is therefore able to provide the adequate quality of English language to meet the requirements for academic publishing. The hereby found grammatical errors were corrected accordingly and marked in red.



**Reviewer #4 (ID: 03722832):** Dear author follow <http://www.prisma-statement.org/> to shape of your review to the best shape.

We thank the reviewer for his valuable recommendation. In our manuscript we reviewed a total of 8 contemporary studies, which were selected and evaluated systematically following the PRISMA standards. They shall outline the current scientific status of invasive pressure derived flow indices to assess myocardial ischemia at the moment of the preparation of the manuscript. However, our review does not completely display an original PRISMA study.

**Reviewer #5 (ID: 02874819):** This review concerns a very interesting but also very specialized field, therefore it mainly concerns a selected population. However it is well written, rather complete for the specific area involved, so it can be accepted in its current form.

**Author:**

We deleted the following sentence in “CLINICAL STUDIES ABOUT THE iFR<sup>®</sup>-MEASUREMENT” since it refers to a congress that already took place:

“A two-year follow up will be presented at the European Society of Cardiology (ESC) congress 2018.”