Introduction to the reviewer responses:

We thank the reviewers for their important comments and constructive advices. In order to be able to address them fully, we have asked the help of two colleagues who provided recent cases they performed with QFR and helped us for the literature review on this topic. They help us polishing our English. We felt normal to include them as co-authors.

The key reviewer's comments appear in Orange type, our commentary and reponses appear in Red type and new additions to the manuscript documents appear in Blue Type.

We thank the reviewers for the time and effort made to analyze our manuscript.

The article is well organized. But it needs polish.

We thank the reviewer for his request that was implemented.

The author is suggested to discuss the difference or explain why IFR appears in the introduction part. We felt necessary to introduce the instantaneous wave free ratio in the introduction, as this invasive tool was the first and most studied non-hyperemic pressure ratio.

Besides, NPHR and NHPR appear in the text, please correct. We thank the reviewer for this accurate comment. We corrected this error. NHPR (Page 3)

The author introduce the definition of FFR, what about theoretical basis of iFR ?

We discussed the theoretical basics of iFR in the first "ratio of instantaneous wave free ratio" paragraph. We explained that iFR is based on the naturally low coronary resistance during the instantaneous wave free period. This period defined upon the ADVISE trial as the interval time comprised between 25% after the onset of the diastole until 5 msec before its end.

The author said that "An hybrid approach to intermediate lesions (DFR 0.85 – 0.95) may be reasonable to maximize data available in clinical decision making and to facilitate appropriate revascularization strategies.' So, I suggested the author discuss the shortage of FFR and IFR, and discuss when to combine other assessment tools and the related clinical significance. We thank the reviewer for this relevant comment that prompts us to further clarify the modalities of the hybrid approach. We have added this paragraph at the page 9 : IV- The Hybrid approach:

In multiple scenarios, the use of FFR or iFR alone may not suffice to take the proper therapeutic decision. Hence, a hybrid approach is useful in some clinical scenarios. Using FFR as the gold standard, NHPR has an average accuracy of 80% resulting in stenoses misclassifications. A combined physiological assessment without adenosine in the first line demonstrated a reduction of the need of intracoronary vasodilator in more than half of the CAD patients in need of functional assessment. Furthermore, the use a 0.86-0.93 cut-off range for iFR improve its positive and negative predictive value to respectively 92% and 91% [63].

The technical aspect of PCI optimization involves proper use of diagnostic and guidance imaging, equipment, techniques, and antithrombotic therapy to achieve optimal patient outcomes. Recently, the value of low post PCI FFR has been linked to poor outcomes related to suboptimal stent placement or remaining disease[78]. In this specific setting, intravascular imaging may be helpful to understand the mechanisms behind inadequate functional improvement. The FFR REACT trial used a post PCI threshold of 0.90 and randomized 291 patients for IVUS or traditional standard of care. This strategy resulted in the improvement

of post PCI FFR in 20% of the vessels with a trend for lower target vessel revascularization in the IVUS guided arm (p=0,06).[79]
Intermediate left main coronary artery lesions can be evaluated more thoroughly with either intracoronary imaging (using intravascular ultrasound (IVUS)) or physiological assessment (using fractional flow reserve (FFR) pressure wire). These invasive tools can provide more detailed information on the anatomical severity and hemodynamic significance of the lesions to be discussed in the heart team to improve the decision of the revascularization strategy and its optimization. Park has reviewed in detail the role of pre and post PCI role of IVUS and FFR are well detailed.[80] The ILITRO-EPIC07 study showed that FFR and iFR had an average agreement of 80%, while IVUS was more likely to match FFR's classification of stenosis significance in discrepant cases. Therefore, from a clinician's viewpoint, the best approach for determining if revascularization can be safely deferred in intermediate left main coronary artery lesions is a combination of IVUS and physiology[49].

I congratulate the authors for an exhaustive review on FFR and NHPR. There has been an adequate literature review on the topic with updated references included in the bibliography. However, the major concern I have is regarding the novelty of this manuscript. The facts that have been included are already known. I would like to see an integrative approach to yield newer applications. I want you to use your thought process and generate newer hypothesis/ the future of this technology in clinical practice. Besides this I would like the inclusion of QFR, which has come a big way and is challenging to replace FFR in cath lab in a few years time thanks to the obvious advantage. Discuss how QFR fairs compared to FFR and NHPR. You can add these studies and include in references:- 1) Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, Liu T, Di Serafino L, Di Girolamo D, Escaned J, Nef H. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. Journal of the American Heart Association. 2018 Jul 17;7(14):e009603. 2) Kasinadhuni G, Batta A, Gawalkar AA, Budakoty S, Gupta A, Vijayvergiya R. Validity and correlation of quantitative flow ratio with fractional flow reserve for assessment of intermediate coronary lesions. Acta Cardiologica. 2022 Apr 5:1-8. 3) Cortés C, Carrasco-Moraleja M, Aparisi A, Rodriguez-Gabella T, Campo A, Gutiérrez H, Julca F, Gómez I, San Román JA, Amat-Santos IJ. Quantitative flow ratio—Meta-analysis and systematic review. Catheterization and Cardiovascular Interventions. 2021 Apr 1;97(5):807-14.
We thank the reviewer for his kindful comment. First, we didn't include the QFR in this review to stay focused on the subject of FFR and NHPR and keep our text as short as possible. but the reviewer is right and the future perspective of functional coronary assessment is based on QFR and CT-FFR.
We included, the following paragraph, at the page 10 and 11, and added two short clinical cases considering the proposed articles to add:
V- Quantitative Flow Ratio and Fractional Flow Reserve Computed Tomography:

More recently, physiological coronary assessment has been evaluated with virtual tools computing the flow ratio. Quantitative flow ratio (QFR) is based on the analysis of two angiography views 25° apart at least with minimal superposition between the main and side branches. The QFR uses a mathematical model, the three-dimensional reconstruction and coronary contrast product progress

in order to determine the coronary flow. The FAVOR trial was the first to assess this technique, and showed significant correlation with FFR (r=0,77; p<0,001) with an 80% accuracy using an FFR threshold of 0,80 [81]. Along with these promising results, the FAVOR II Europe-Japan Study found that QFR is superior to angiographic assessment of intermediary coronary artery stenosis using FFR as standard reference [82]. Kasinadhuni et al. showed that QFR has a superior diagnostic performance compared to the benchmark FFR in evaluating intermediate lesions physiologically outperforming the anatomical percentage diameter stenosis with a significant difference ($p < 0.001$) [83].
QFR and FFR have excellent consistency and alignment. The ability of QFR to determine the functional impact of coronary disease has been demonstrated in the meta-analysis and systematic review of Cortés et al [84]. This new tool, and a similar one, vFFR implemented in the CAAS Worstation (Pie Medical Imaging, Maastricht, the Netherlands) are independent predictors for MACE with beneficial effect of PCI for low QFR / vFFR values[85, 86].

The SYNTAX III REVOLUTION study showed that using Computed coronary tomography angiography to decide between CABG and PCI for coronary artery disease, based on the predicted four-year mortality as indicated by the SYNTAX score II, resulted in high agreement (93%) in treatment decisions, with an "almost perfect kappa" of 0.82, compared to decisions made using ICA [87].
FFR-Computed Tomography (FFR-CT) allows for the measurement of flow across the entire coronary artery bed unlike the usual method which assess the functional significance of a specific coronary stenosis and its upstream segments [88].
These new concepts open new tracks for a better risk stratification and prognosis prediction of patients presenting with coronary artery disease. Their use is increasing in the context of stable CAD for the guidance of percutaneous interventions, but some authors have demonstrated the prognostic implication of a post interventional pan-coronary-QFR evaluation in patients with ACS [89].
We hypothesize that further improvement of these techniques might help the physicians to discriminate atherosclerotic NSTE-ACS from type II Myocardial infarction and myocardial infarction with non-obstructive coronary disease.
A hybrid approach, with a combined use of both anatomical (IVUS) and functional methods to determine the significance of coronary stenosis, could provide a more comprehensive and accurate assessment enabling the operators to take more targeted and individualized decisions. However, the hybrid approach does require additional imaging and testing, which can increase the cost and complexity of the evaluation. Using QFR and IVUS simultaneously, or FFR-CT before, seems appealing as they combined only one invasive evaluation with a noninvasive one, lowering the cost.

We illustrate this concept in a recent clinical case we performed. A stable patient with suspected myocardial ischemia after dobutamine stress test had a coronary angiogram demonstrating a LAD with a moderate long lesion in the proximal and mid part (figure 4) that was evaluated by QFR at 0.83 (figure 5). Regarding these intermediate values, a complementary IVUS evaluation was performed (figure 6) showing a non-significant lesion with a minimal lumen area of was 4.7 mm^2.

The good agreement between QFR and FFR is illustrated in another case summarized on Figures 7 to 9. On the coronary angiogram of a patient with recurrent clinical symptoms, we noticed multiple intermediates lesions in the proximal, mid, and distal LAD (Figure 7).
The FFR was positive in the distal LAD at 0,78 and also the DFR was 0,86 (figure 8). The QFRof 0.75 was well aligned with these measurements (figure 9). The relationship between QFR and clinical outcomes, and its cost-effectiveness, requires further prospective validation.

During our review, we revised the figure legend that did not include the fifth table (page 24) and corrected the caption of the table 4, which inadvertently specified table 4 instead of table 5 (page 22)